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Institute of Translational Medicine

Chemotherapy Induced Peripheral Neuropathy:

Clinical Aspects and Molecular Genetics

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Medicine by Joanne Cliff

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Disclaimer: The entirety of the work presented in this thesis, unless otherwise stated, is that of the author.

ABSTRACT

As the treatment of cancer evolves, complexity is increasing with the range of and number therapies now being offered to patients. Patients are living with or beyond cancer for longer periods of time. Cancer survivorship issues are therefore gaining greater importance, and long term toxicities from cancer therapies must be acknowledged and addressed. One such adverse effect is chemotherapy induced peripheral neuropathy (CIPN). Many widely used cytotoxic agents lead to peripheral neuropathy in a proportion of patients. For some, the neuropathy settles after completion of treatment but for a small, but not insignificant minority, the neuropathy persists. The aims of this project were to systematically explore the clinical and molecular genetic risk factors, and effect on quality of life, of this potentially debilitating toxicity.

Chapter 1 comprises an introduction to the topic including a narrative review of clinical risk factors. Choice of agent, duration of infusion and cumulative dose affect the development of CIPN. Patient-related factors are less clear, but body mass index and race appear to be of particular interest as possible determinants.

Chapter 2 includes systematic reviews of the impact of diabetes and alcohol intake on risk of CIPN which identified a number of studies but meta-analysis was not possible and no definitive conclusion on effect could be drawn as findings from the included studies were contradictory.

Chapter 3 describes a comprehensive systematic review of pharmacogenetic studies related to the risk of developing CIPN. This identified 93 studies for inclusion with a median sample size of 118 patients. *GSTP Ile105Val* was the most commonly investigated SNP, with SNPs in the excision repair genes, ABC transporter genes and *CYP 3A4, 3A5* and *2C8* genes also frequently investigated. Meta-analysis was carried out where possible, the majority of which showed no significant association. *CYP3A4*22* did show significant association but this data was based on two cohorts within the same study. Many studies however were not eligible for inclusion in meta-analysis due to lack of sufficient data presented. Pharmacogenetic studies in this field are fraught with methodological flaws. Accurate phenotypic definition and recognising potential clinical confounding factors in research populations is key to improving the quality of research.

Chapter 4 presents a candidate gene study in both a taxane- and an oxaliplatin-treated cohort of patients 187 taxane- treated patients were included for genotype analysis. Based on the systematic review, seven single nucleotide polymorphisms (SNPs) were identified for investigation. However, no significant associations were identified for CYP2C8*3, CYP3A4*22, *EPHA4, EPHA5, EPHA6, FGD4,* and *XKR4*. For the oxaliplatin cohort of 120 patients, three SNPs, *ACYP2 rs843748*, *FARS2 rs17140129* and *TAC1 rs10486003,* were investigated based on previous GWAS results. Again, no significant effects were seen in this population. A strength of this pharmacogenetic study was use of both medical assessment of CIPN and patient reported outcome to support phenotypic definition.

The quality of life study is presented in chapter 5 and confirmed a statistically significant correlation between patient reported neuropathy scores and both quality of life and functional measures. In the paclitaxel cohort, the sensory score was negatively correlated with a functional score at 6 months post-chemotherapy. In the oxaliplatin cohort, at the end of the treatment time point for those who received >6 cycles, there was a significant negative correlation between the sensory score and both functional and global QoL scores. More consistently over time, however, correlations with QoL and functional scores in those who scored more highly on the motor aspects of the CIPN20 module were seen. Persistent neuropathy leading to higher scores in the motor aspects of the CIPN20 showed a statistically significant difference in functional score (p=0.002) and global QoL score (p=0.026) at the 18 month time-point.

Finally, chapter 6 comprises discussion of the work and concludes that future work needs to build a clinical and genetic model upon which to assess an individual's risk for development of this toxicity which can impact quality of life and function many months and years after treatment. Improving assessment and standardising outcome measurements, potentially through the development of consortia to further the pharmacogenetic research aspect of cancer drug safety is key to improving the evidence base to build risk models which may start to improve individualisation of treatment and develop a more personalised assessment of risk of harm.

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CHAPTER 1

INTRODUCTION

Advances in oncology mean that patients are living longer with a cancer diagnosis following treatment. As a consequence, survivorship issues are becoming increasingly important and there is a growing need to consider the long term adverse effects of cancer treatment. Chemotherapy induced peripheral neuropathy (CIPN) is a common adverse effect during treatment, is a common reason for dose reduction or early cessation of therapy and, for a significant number of patients, it can persist for a long period of time following completion of treatment with significant impact on function. The mechanism of CIPN is poorly understood but there is emerging evidence that susceptibility to drug induced neurotoxicity can be predicted by an individual's genotype.

Agents associated with CIPN include the taxanes, platinums and vinca alkaloids. The taxanes, largely docetaxel and paclitaxel, are widely used in clinical practice in the treatment of breast cancer, gynaecological cancers and prostate cancer. Taxane induced peripheral neuropathy can affect approximately 50-60% of patients with up to 33% of patients experiencing more severe neuropathy (NCI CTC grade 3-4) (2). A study investigating dose delivery of taxane chemotherapy in women with early breast cancer found that 37% of all dose delay/ dose reduction or early discontinuation events were due to CIPN (3).

Of the platinum drugs, it is largely cisplatin and oxaliplatin which are associated with CIPN, with carboplatin having very little associated neuropathy. Myelosuppression instead is the main dose limiting toxicity of carboplatin. Cisplatin is used in the treatment of many cancers, forming the basis of chemotherapy for lung cancer, germ cell tumours, head and neck and cervical cancers. Oxaliplatin on the other hand has been associated with two distinct forms of neurotoxic manifestations: acute, transient symptoms are due to peripheral sensory and motor neurone hypersensitivity and occur in up to 90% of patients (4); and cumulative more chronic peripheral neuropathy that interferes with function occurring in 15-20% of patients (5, 6). Oxaliplatin is used in the treatment of colorectal, oesophageal and gastric cancers.

The vinca alkaloids have a major role in the treatment of haematological malignancies both in adults and children, as well as playing a role in sarcoma, breast and lung cancer therapy. Vincristine, in particular, is associated with neurotoxicity, one of its most important dose limiting effects.

1.1 PRESENTATION, PHARMACOLOGY AND PATHOPHYSIOLOGY OF CIPN

CIPN is peripheral nerve damage caused by cytotoxic systemic anti-cancer therapies. It most commonly affects large and small sensory nerves and results in loss of sensation, paraesthesia or neuropathic pain initially in the fingers and toes, but can progress to affect more of the distal limbs in a 'glove and stocking' pattern. Motor fibres can also be affected, but this is less common. Vincristine can also cause damage to autonomic nerves and can result in constipation or urinary retention (7). Sensory impairment can lead to difficulty in carrying out simple tasks such as doing up buttons or holding a pen and in more severe cases, can lead to dropping objects, difficulty walking and falls. Neuropathic pain may co-exist with other changes in sensation. Symptoms may be transient after doses of neurotoxic chemotherapy agents and settle completely after treatment, or they may also persist between cycles, accumulating to becoming chronic and lasting long after chemotherapy has finished. In the case of platinum chemotherapy, the toxicity may display 'coasting', where symptoms may become more apparent after completion of treatment (8). Often there is at least some reversal of symptoms within 12 months after treatment (9) but there are a significant minority of patients who have ongoing symptoms for much longer after therapy has finished (10-12).

1.1.1 Platinum agents

The structures of the platinum agents are shown in figure 1.1. The primary mechanism of platinum cytotoxicity is through covalent binding of reactive platinum species to DNA resulting in distortion, failure of replication and subsequent cell death (13). It is believed that cisplatin enters cells through a combination of passive diffusion and the copper transporter hCtr1 pathway (14).

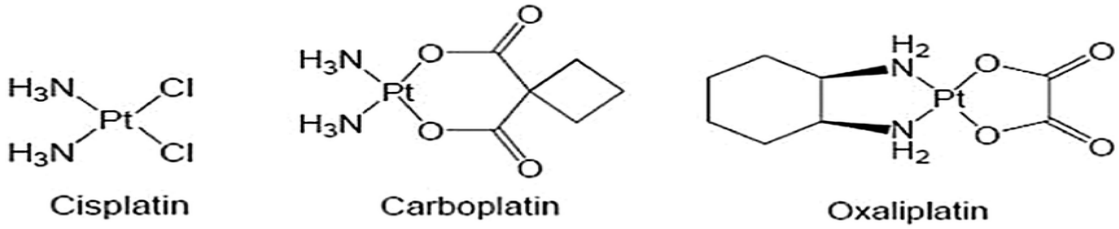


Figure 1.1 Structure of the platinum drugs in common oncology use (http://pubs.rsc.org/EN/content/articlehtml/2014/cc/c4cc02254h?page=search)

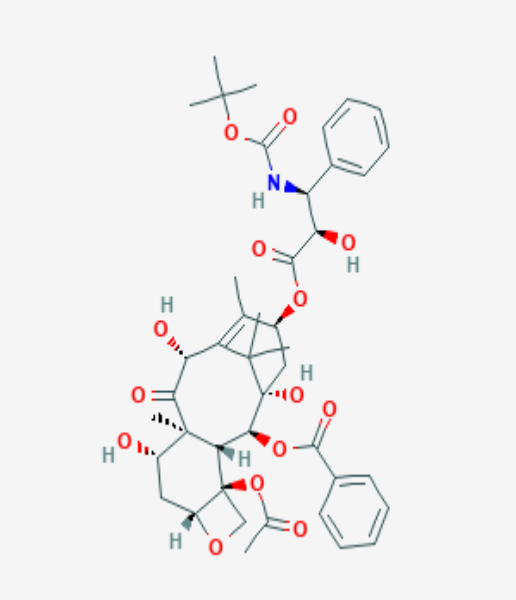
The main resistance mechanisms include failure of accumulation within the cell, increased detoxification (mainly by glutathione) and enhanced repair mechanisms (14). Platinum neurotoxicity occurs due to damage to the dorsal root ganglion (DRG). It has been shown that platinum drugs accumulate here (15, 16) and may cause apoptosis through DNA adduct formation in sensory neurones (17). There is *in vitro* evidence of Ctr transporters in neuronal cells of the dorsal root ganglion in rats (18). In oxaliplatin induced acute neurotoxicity, there are also features of axonal hyperexcitability with evidence of alterations in voltage-gated calcium channel function (19) and sodium channels (20). Understanding of factors that may predispose to platinum accumulation, efflux and increased adduct formation are incomplete. A number of other transporters may play a role in accumulation and efflux of platinum agents in and out of various tissues including the ABC transporters, OCT1, OCT2 and MATE (21) . Repair of platinum-related DNA damage occurs predominantly through the nucleotide excision repair pathway with a smaller contribution from the base excision pathway. Various genetic variants in molecules such as excision repair cross- complementing group 1 (ERCC1), excision repair cross-complementing group 2 (ERCC2) and x-ray repair cross-complementing protein 1 (XRCC1) have been explored as possible resistance mechanisms to the platinum drugs but with largely contradictory results, and so no definite differential response or outcome with genetic variants is recognised (22). However, data for polymorphisms in XRCC1 in Asian populations is rather more suggestive of a clinically important effect (23). Other potential important molecular repair pathways are less well studied at present.

1.1.2 Taxanes

The taxanes, largely paclitaxel and docetaxel, in widespread clinical use, are both metabolised in the liver. The structures of these two commonly used drugs are shown in figure 1.2. Both are substrates for CYP3A4 and CYP1B1 (24-26); paclitaxel is also metabolised by CYP2C8 (27) and docetaxel by CYP3A5 (28). They are transported by the ATP-binding cassette transporters ABCB1, ABCG2, ABCC1 and ABCC2, and in particular, OATP1B3 has been found to be a key molecule in transporting both taxane drugs into hepatocytes (26). Some studies have shown that variants in genes encoding for the above proteins have resulted in different taxane pharmacokinetics (29-31) whereas others have not shown evidence of change in paclitaxel clearance (32, 33). The taxanes have been hypothesized to cause neuropathy via several mechanisms. Their main mechanism of cytotoxicity is to affect microtubule dynamics by inhibiting tubulin depolymerisation. Microtubules are made up of □□ and □- tubulin heterodimers, and whilst most data suggest mutation of the tubulin-encoding TUBB gene is not a resistance mechanism, overexpression of tubulins may be (26). The process of altering microtubule dynamics is also thought to be a mechanism of neurotoxicity as interference with microtubules in the axons of nerves may disrupt axonal transport (34, 35). It is also thought that taxanes may also cause damage at the DRG (36). A further theory is that taxanes induce damage in mitochondria leading to energy failure (37). Reactive oxygen species in sensory nerves have also been proposed as a mechanism for ongoing paclitaxel-induced painful neuropathy (38).

Paclitaxel is hydrophobic and is solubilised in polyoxyethylated castor oil (Cremaphor EL) and ethanol. These vehicles are associated with some of the hypersensitivity reactions seen in a proportion of patients treated with paclitaxel. Nab- paclitaxel is albumin-bound paclitaxel and overcomes some of the problems of hypersensitivity and drug delivery.

Docetaxel



Paclitaxel

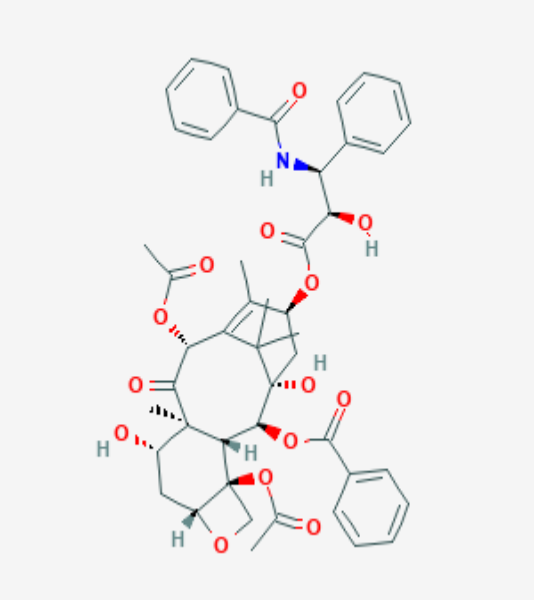


Figure 1.2 Structures of docetaxel and paclitaxel

(https://pubchem.ncbi.nlm.nih.gov/compound/)

1.1.3 Vincristine

Like the taxanes, vincristine is also primarily metabolised by the CYP3A system, being a substrate for both CYP3A4 and CYP3A5. Different variant alleles exist for expression of these enzymes and CYP3A5 production relies on the presence of at least one copy of the CYP3A5*1 allele. Absence of this allele results in no CYP3A5 production and reliance on the significantly less efficient CYP3A4 for metabolism of vincristine. Figure 1.3 shows the structure of vincristine.

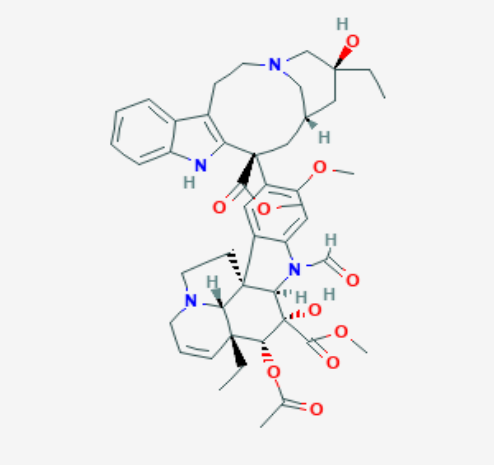


Figure 1.3 Structure of vincristine

(https://pubchem.ncbi.nlm.nih.gov/compound/5978#section=2D-Structure)

There is a marked difference in expression of CYP3A5 between racial groups with African Americans being high expressors (approximately 75%), East Asians intermediate (approximately 47% of individuals are expressors) and Caucasians having low levels of expression (around 19% of Caucasians) (39). The CYP3A5*3 is the most common allele in Caucasians and results in a splice defect and ineffective enzyme production (40). Racial differences in the outcomes of vincristine-containing leukaemia therapy have led to speculation that CYP3A5 expression may play a clinically significant role in the pharmacokinetics of vincristine. This difference in CYP3A5 expression was retrospectively investigated when it was recognised that African American children had reduced survival rate in an acute lymphoblastic leukaemia (ALL) study. However, CYP3A5 expression was not significantly related to relapse rate (41). Renbarger et al also demonstrated a significantly lower neurotoxicity rate in vincristine-,treated African American children compared to Caucasians (42). Membrane transporters including ABCB1, ABCC1, ABCC2 and ABCC3 (43-45) have roles in vincristine transport and elimination. Biliary excretion of vincristine is mediated by ABCB1 and ABCC2 and transport into the blood occurs through ABCC1 (46). As with other agents the mechanism of neurotoxicity is not fully understood, but similarly, neurone damage at the DRG (47) is recognised, as well as there being evidence that interference with both antegrade and retrograde transport in axoplasm due to its effects on microtubules is contributory (34, 48).

1.1.14 Epothilones

The epothilones are non-taxane microtubule stabilising agents and produce mitotic arrest with a similar mechanism to the taxane drugs (49). They are not in widespread standard use in UK oncology practice but ixabepilone has been reported to have some activity in hormone refractory prostate cancer (50) and has been shown to have some efficacy in metastatic breast cancer (51). Like the taxanes, they can produce a primarily sensory peripheral neuropathy. It is thought that the predominant mechanism of neurotoxicity is through interference with axonal transport in effected neurons (52). As their current use is very limited at present, the epothilones, whilst mentioned in this thesis are not a topic of focus.

1.2 INCIDENCE AND RISK FACTORS FOR DEVELOPMENT OF CIPN

1.2.1 CIPN in different patient cohorts according to primary cancer

Many studies include potentially neurotoxic drugs, both as single agent treatments and in different chemotherapy combinations, and will present data on toxicities including peripheral neuropathy. There are far too many studies to reference all so for the summary presented below, in general the papers quoted refer to the seminal studies which led to the standard inclusion of that drug in the treatment of the relevant cancer type.

CIPN in patients treated for gynaecological cancer

Paclitaxel is part of the standard treatment for ovarian cancer in patients whose fitness permits, alongside a platinum, usually carboplatin. It is used in doublet therapy in first line therapy, platinum-sensitive relapse and it is also utilised in a weekly regimen as a single agent in platinum-resistant disease. Of the large-scale trials which have confirmed the use of paclitaxel in ovarian cancer, ICON 3 randomised 1421 patients to receive either single agent carboplatin or carboplatin with paclitaxel 175mg/m^2 with the result that 19% of those receiving taxane experienced grade 2-3 sensory neuropathy while 6% experienced grade 2-3 motor neuropathy (in comparison with 1% and <1%,

respectively, on carboplatin alone) (53). Similarly, in a study conducted by the same group, paclitaxel was added to conventional platinum- based chemotherapy in the relapse setting. A similar increase in grade 2-4 neurological toxicity (1% with platinum alone compared to 20% with concurrent paclitaxel) was seen (54). The SCOTROC1 trial found a higher incidence with 30% of patients on the paclitaxel-carboplatin arm experiencing grade 2-4 sensory neuropathy with the same dose and schedule of paclitaxel. They found that 78% of patients experienced any grade of neurosensory toxicity. Many patients who experience neuropathy during treatment will have resolution of their symptoms. However, from clinical experience we know that a significant proportion of patients experience persistent symptoms after treatment. One study that looked at a group of 120 patients treated with carboplatin and paclitaxel found that of the 65 (54%) patients who developed at least grade 1 neuropathy during chemotherapy:

- 9 patients (15% of the total treated) had residual neuropathy symptoms at assessment more than 6 months after completion of paclitaxel therapy (55); and
- 14% of the treated population had residual neuropathy at one year and 11% at two years.

Nab- paclitaxel is used far less commonly in gynaecological malignancies that paclitaxel. However, it does sometimes play a role as single agent therapy in platinum resistant or refractory disease. Sensory neuropathy has been reported in approximately 40% of patients with grade 3 neuropathy relatively infrequent in around 2% of patients (56).

CIPN in patients treated for breast cancer

Patients with early breast cancer who require neoadjuvant chemotherapy frequently receive a taxane-containing regimen, either docetaxel three-weekly or weekly paclitaxel. Those who require adjuvant chemotherapy after surgery may receive a taxane-containing regimen, particularly if they were found to have node positive disease. The TACT trial which investigated the addition of docetaxel to adjuvant chemotherapy in 4162 women with early breast cancer found a 5% rate of grade 3-4 neuropathy (57). A study which was performed alongside a phase III trial in patients with early breast cancer receiving three cycles of three-weekly adjuvant docetaxel (100mg/m^2 or 75mg/m^2) identified 34% of patients experiencing grade 2-4 neuropathy,

although 5% of patients had pre-existing neuropathy (58). Eckhoff et al also investigated the persistence of neuropathy after adjuvant docetaxel treatment and reported a rate of 15% persistence 1-3 years after completion of therapy (59). Patients with advanced breast cancer are frequently treated with taxanes; in this population a phase III trial of 3 weekly docetaxel versus doxorubicin showed a 42.8% and 5% rate of any and grade 3-4 sensory neuropathy, respectively, in the docetaxel- treated patients (60). Nab-paclitaxel is sometimes used in patients with metastatic breast cancer, most commonly in those who experience hypersensitivity to paclitaxel. It's use is associated with a 10% rate of grade 3 sensory peripheral neuropathy which has been reported to reduce to grade 1-2 neuropathy with withholding of drug in a median of approximately 22 days (61).

CIPN in patients treated for prostate cancer

Docetaxel is frequently used in the management of castrate-resistant prostate cancer based on a seminal trial showing improved quality of life over mitoxantrone. A 30% incidence of any grade neuropathy was reported with the now standard three-weekly regimen of docetaxel 75mg/m^2 (62). A further trial using the same standard regimen of docetaxel as the control arm (598 patients) with placebo similarly showed a rate of 26% for all grades of CIPN and a 3% incidence of grade 3-4 neuropathy (63).

CIPN in patients treated for gastrointestinal cancer

Oxaliplatin is integral to the management of both early stage operable and advanced colorectal adenocarcinoma (CRC). It has been shown to improve response rates and progression free survival in the advanced setting compared to a fluoropyrimidine alone but causes a significant degree of neurological toxicity. DeGramont et al reported that 68% get any grade of paraesthesiae in their seminal phase III trial with oxaliplatin 85mg/m^2 delivered two-weekly with 5-fluorouracil (5FU), with 18.2% grade 3-4 sensory disturbance. Much of this was transient cold-related dysaethesia but they reported a 16% rate of cumulative paraesthesiae interfering with function. There was an improvement from grade 3 neuropathy over a median of 13 weeks in three quarters of the patients (5). Goldberg et al also reported an 18% risk of grade 3 paraesthesiae in a key phase III trial of oxaliplatin use in advanced CRC (64). A further important phase III trial comparing different sequencing of combination regimens (FOLFIRI then FOLFOX or

vice versa) reported a higher rate of neuropathy with almost universal experience of some degree of neurotoxicity (>90%) during oxaliplatin therapy and an incidence of grade 3 neuropathy of 34% in those receiving FOLFOX6 (oxaliplatin at 100mg/m^2 administered two-weekly) as first line therapy. They state that 13% of these patients had resolution to <grade 3 neuropathy 1 month after completion of therapy, and 31% improved from grade 3 neuropathy within three months. This implies that 21 of 111 patients had grade 3 neuropathy which lasted more than 3 months post treatment (65), a not insignificant statistic.

The MOSAIC trial confirmed a role for oxaliplatin as adjuvant treatment for resected colon cancer with a significant improvement in disease-free survival. Oxaliplatin was delivered at a dose of 85mg/m^2 two-weekly in combination with 5FU/LV. 92.1% experienced neuropathy of any grade, 12.4% developed grade 3 neuropathy during treatment and a further 12 patients developed grade 3 neuropathy after treatment. In total, 1.1% of patients had persistent grade 3 neuropathy at 1 year (66).

A retrospective study of 188 patients treated with CAPOX outside of a trial setting demonstrated a rate of 16% grade 3-4 chronic neuropathy in individuals receiving adjuvant treatment, and 4% in palliatively-treated patients. At 12 months post treatment, 35% of 85 adjuvant-treatment patients were still experiencing neuropathy symptoms (67).

For patients with gastric and oesophageal adenocarcinoma, CIPN has long been an adverse effect of treatment as it has generally involved platinum- based therapy. Treatment has evolved from cisplatin/5FU to ECF (epirubicin/cisplatin/5FU) to now many patients receiving EOX (epirubicin/ oxaliplatin/capecitabine) on the back of a large non-inferiority phase III trial by Cunningham et al (68). With the cisplatin combinations, peripheral neuropathy was found to affect 30-40% of patients with <2% experiencing grade 3-4 neurotoxicity. With the oxaliplatin triplets, this increased to around 80% of patients experiencing any grade neuropathy and 4.4% and 8.4% of patients experiencing grade 3-4 neuropathy receiving EOX or EOF, respectively. This figure is lower than in some of the CRC trials stated above. The differences are possibly

due to a higher median number of cycles received by the CRC patients, the different regimens and different patient populations.

CIPN in patients treated for testicular germ cell tumour

Potentially neurotoxic drugs are used in the primary treatment of testicular germ cell tumours (GCTs) with cisplatin being a vital component of combination chemotherapy. Cisplatin, vinblastine and/or paclitaxel are frequently used in second line treatment where necessary. In a cross-sectional study of 1409 survivors of testicular cancer in Norway at a median of 10.7 years post orchidectomy (range 4-21), 29% of all men who had received chemotherapy reported paraesthesiae in hands or feet as a major symptom (69). Similarly in the UK, a study assessed 730 patients for evidence of ongoing neuropathy >3 years after treatment. On clinical assessment, evidence of neuropathy was found in 20.3% of men who had received chemotherapy and 11.8% of those completing a subjective assessment reported neuropathy as an ongoing significant issue (70).

CIPN in patients treated for haematological cancer

Vincristine is a key drug in the combination chemotherapy regimens used to treat acute lymphoblastic leukaemia (ALL). This is a common paediatric malignancy and cure rates of around 85% can be achieved. Maintaining dose intensity is important and this can be compromised by peripheral neuropathy which is the primary dose limiting toxicity of vincristine. Clinically important neuropathy occurs in around 25% of children undergoing ALL treatment protocols (71, 72).

Vincristine is routinely dose-capped to 2mg per dose because of the occurrence of neurotoxicity but evidence suggests a large inter-individual variability in drug exposure (73). Vincristine is an integral part of the R-CHOP regimen which is commonly used for non-Hodgkin lymphoma (NHL). Peripheral neuropathy can occur in up to 44% of patients, but grade 3-4 neuropathy is not often seen (74)

Vinblastine is used in the treatment of Hodgkins lymphoma but neuropathy is less of an issue here. Severe neurotoxicity is not usually encountered and dose reduction due to CIPN is far less frequent (75).

1.2.2 Age and chemotherapy induced peripheral neuropathy

Taxanes

Most of the literature shows no effect of age on the development of CIPN in both retrospective (76-79) and prospective studies (80-82). Exceptions to this include one study which reported that patients younger than 50 years showed a significantly higher neurotoxicity rate than those older than 50. However, this was a very mixed group of patients with different primaries and different paclitaxel schedules (83). A further retrospective study suggested that CIPN related to adjuvant paclitaxel in breast cancer patients persisted for longer in patients over 60 years of age. However, the study design, involving case-note review only for grading and persistence of neuropathy, has to be taken into account (84). Weak evidence that older patients are at increased risk of sensory neuropathy was seen in a further paclitaxel study but this does not appear to be clinically significant (HR per year= 1.02, 95% CI 1.00-1.05, p =0.082) (85). A study presented in abstract form reported an increased incidence of paclitaxel-induced neuropathy with increasing age with a 12.9% increase in risk for every decade (86). However, this really stands out alone as the only study suggesting such a large impact of age.

Oxaliplatin

Similarly with oxaliplatin, much of the literature reports no significant difference both in prospective (5, 87-90) and retrospective studies (78, 91-95). In a prospective study of 366 patients performed to assess the influence of baseline clinical characteristics in the risk of developing severe oxaliplatin induced chronic peripheral neurotoxicity (defined as grade 3 PN or grade 2 PN persisting for greater than 7 days), patients in the older age group (55 years or over) demonstrated an increased risk on univariate analysis, but this was not upheld in multivariate analysis (96). Vincenzi et al, in their retrospective cohort of 169 FOLFOX4-treated adjuvant colorectal cancer patients, showed no evidence of association between the development of CIPN and age, but did note a longer duration of symptoms in younger patients ($\leq$60 years) after adjustment for a group of other clinical parameters (97).

1.2.3 Gender and chemotherapy induced peripheral neuropathy

The weight of evidence would suggest that there is no difference in the occurrence of CIPN based on gender for either taxanes (81), oxaliplatin (89-91, 94-96) or cisplatin (98). There is relatively little comparative evidence within taxane-based studies as many have been carried out in breast, ovarian or prostate cancer patient cohorts, which by their very nature are almost universally single-gender studies.

A prospective study of 200 colorectal cancer patients undergoing oxaliplatin- based chemotherapy found that male patients were more likely to develop grade 3 or higher neuropathy than female patients. They excluded patients with pre-existing PN, diabetes, alcohol excess or any medications which may cause PN. This finding did not persist in multivariate analysis and the authors speculated that it may be related to the fact that men received higher cumulative doses (99).

A retrospective analysis of prospectively collected data demonstrated that significantly more females than males developed any grade of neurotoxicity with taxane-based treatments in both exploratory and validation cohorts (67% of females vs 33% of males and 65% of females vs 29% of males in cohort sizes of 261 and 239 patients, respectively). Patients were being treated for any solid malignancy and there was no adjustment for schedule, which was weekly or 3 weekly, or differing dosages, and so there was a significant risk of confounding (100).

1.2.3 Ethnicity and chemotherapy- induced peripheral neuropathy

A retrospective review of 123 breast cancer patients who had received adjuvant or neoadjuvant taxanes showed that a greater proportion of African American patients (53%) had dose reductions due to CIPN than Caucasian or 'other' patients (22% combined) (101). A paclitaxel study in breast cancer patients noted a similar increased risk in African American patients (HR 2.1, $p=4.5x\ 10^{11}$) (86). A study designed to review participants recruited to a number of prospective treatment trials and compare

tolerability of cisplatin and doxorubicin in white and black women with endometrial cancer did not show a difference in neurological toxicity (102).

The most notable discrepancy in different racial groups is that reported in vincristine-treated paediatric ALL patients. A relatively small, retrospective study reported a 34.8% risk of vincristine neuropathy in Caucasian children compared to a rate of 4.8% in African American patients, offering a hypothesis that this could be due to differential CYP3A5 expression (42) and some genetics studies support this theory (71). The sheer magnitude of the differences seen in both taxanes and vincristine in racial difference would appear to warrant further investigation.

1.2.4 Body mass index and chemotherapy induced peripheral neuropathy

Body mass index has only been addressed as a potential risk factor for CIPN in a small number of studies but there is some evidence that raised BMI may be associated with increased risk of CIPN. In taxane-treated patients, a case-control study with 150 women treated with three-weekly docetaxel found that of the 75 women developing grade 2 or greater CIPN, 25% had a BMI of 30 or greater compared with 8% of those in the control group (p=0.008) (103). Similarly, in a large cohort study of 6248 patients involved in one of four prospective randomised controlled trials, patients with a BMI in the overweight or obese range were found to have an increased risk of $\geq$grade 2 neuropathy (104). A Danish trial cohort study however showed no evidence of association with BMI in a similar, although small, breast cancer population (105).

In oxaliplatin-treated patients, a prospective study of 102 patients treated with adjuvant CAPOX demonstrated a HR 3.69 (1.2-11.27, p=0.01) of developing grade 2 or greater chronic peripheral neuropathy in patients with a BMI $\geq$25 (5 of 66 patients with BMI <25 compared with 9 of 36 patients with BMI $\geq$ 25) (106). A further two studies have shown an association with increased neuropathy with oxaliplatin and increased body surface area. The first, a prospective study of 366 patients receiving treatment for colon cancer showed a difference in the risk of developing severe oxaliplatin induced chronic neuropathy associated with increased body surface area on univariate analysis,

although this was not observed with multivariate analysis (96). The second was a retrospective study investigating risk factors for developing CIPN with modified FOLFOX6. This study demonstrated no effect of BMI on multivariate analysis but an increased risk of developing both acute and chronic oxaliplatin-induced neuropathy associated with body surface area (BSA) >2.0m^2 (91).

American Society of Clinical Oncology guidelines suggest that patient's BSA should be calculated according to actual body weight due to evidence of worse outcome if dose capping or ideal body weight is utilised (107). If an increased risk of CIPN exists, as some studies suggest, there is a possibility that there could be issues with specific drugs, such as taxanes, leading to a hypothesis that perhaps BSA may not be the ideal way of calculating dose for those with high BMI. It also raises questions about the potential contribution of undiagnosed diabetes being possibly more prevalent in an obese population and the uncertain risk this may confer.

1.2.5 Other comorbidities

The role of other co-existent pathology is uncertain. A number of other pathologies can cause peripheral neuropathy separately from drug-induced peripheral neuropathy such as CIPN. Such conditions include diabetes mellitus, vitamin deficiencies, autoimmune diseases and alcohol excess. Both diabetes and alcohol excess have been explored and their influence on development of CIPN is not conclusive (76, 97, 101, 103, 108). These factors are evaluated in greater depth in chapter 2.

1.2.6 Differential neurotoxicity of different drugs

Docetaxel and paclitaxel are clearly similar in their mechanism of action and have similar indications. Comparisons of the two drugs in trials in uniform populations have consistently demonstrated paclitaxel to be the more neurotoxic agent. Docetaxel/ carboplatin versus paclitaxel/ carboplatin as first line therapy for epithelial ovarian cancer or primary peritoneal cancer demonstrated grade 2 or greater sensory neuropathy in 11% versus 30% in the docetaxel and paclitaxel arms respectively (109). Other studies using similar schedules of the two drugs in comparable populations agree with these findings (110-112).

Oxaliplatin has been found to be more neurotoxic than cisplatin (113) although the cumulative neurotoxicity with both drugs is similar and both can demonstrate coasting, a phenomenon where the neurotoxicity can actually worsen after the final dose of drug. Vincristine is the most neurotoxic of the vinca alkaloids with doses being capped due to increased prevalence of this toxicity >2mg (total dose per cycle). Of the neurotoxic cytotoxic agents, it is the most likely drug to cause autonomic neuropathy.

1.2.7 Effect of cumulative dose on development of CIPN

There certainly seems to be a dose-response with the development of CIPN with higher cumulative doses increasing the risk of its occurrence (80, 81, 91, 92, 114-116). However, it has also been shown that those individuals susceptible to CIPN can be liable to receiving lower total cumulative doses due to early cessation and dose reductions (3, 103). The dose per cycle when given at the same frequency can affect occurrence, as reported in the case of paclitaxel with doses of 250mg/m^2 given three-weekly associated with grade 3-4 neuropathy rates in the order of 20-35% whereas those with doses of <200mg/m^2 are in the range of 5-12% (2). Similarly rates of grade 3-4 neuropathy have been reported to be as high as 17% with docetaxel 100mg/m^2 compared to 2-4% with docetaxel 75mg/m^2 (117). It is not clear that the same is true of cisplatin in terms of dose per cycle, but the effect of cumulative dose is accepted and

most patients receiving 300-450mg/m^2 will develop at least some CIPN (118). For vincristine it is accepted that neurotoxicity is the main dose limiting toxicity and doses per cycle are capped for this reason.

1.2.8 Drug delivery and development of CIPN: Duration of infusion

Paclitaxel

Duration of infusion has mainly been studied in the administration of paclitaxel both for investigating differential effectiveness and tolerability. A Cochrane review published in 2011 (119) showed that a 3- hour infusion was associated with more neurosensory changes compared to those receiving 24-hour infusions with a risk ratio of 1.26 (95% CI 1.09-1.46). They used pooled data from three studies, two in breast cancer patients (120, 121) and one in ovarian cancer (122). However, in one of these studies whilst all patients commenced on 175mg/m^2, the protocol allowed escalation of dose and this important clinical variable was therefore not uniform (120).

Comparison of 3-hour versus 96-hour infusions, in one study reported increased neuropathy with the shorter infusion, but this was given at a significantly higher dose than the 96-hour infusion. Clearly such a prolonged infusion has significant practical disadvantages. In addition, an increased risk of myelosuppression was also found with such administration (123).

24-hour versus 96-hour infusions have been investigated. One study showed no evidence of a difference in the occurrence in peripheral neuropathy in a randomised trial of 324 patients. However this was complicated by a slight difference in dose with a lower dose given with the longer infusion and concurrent treatment with cisplatin, albeit the cisplatin treatment was uniform (124).

Shorter infusion durations have been investigated. One-hour versus three-hour infusions have been looked at in the context of weekly single agent paclitaxel for metastatic cancer. No difference was seen in the occurrence of CIPN as defined by change in the PNP score (81). Overall, it would appear that paclitaxel infused over 24

hours rather than shorter durations, results in less neuropathy but this is at the expense of increased inconvenience and increased myelosuppression.

Oxaliplatin

For oxaliplatin, one identified study has compared administering oxaliplatin 85mg/m^2 over 6 hours compared with 2 hours in a randomised trial involving 64 patients. Other treatment factors were standardised. Reduction in neurotoxicity was assessed by the oxaliplatin-specific scale as the primary end point and the sample size was calculated accordingly. The longer infusion was associated with a reduced incidence of acute neurotoxicity (28.1% vs 59.3% grade $\geq$ 2 neuropathy) (125).

1.2.9 Scheduling of drug

Different drug scheduling has been studied, especially in the case of the taxanes with lower more frequent doses being compared to higher, less frequent dosing. Largely these studies have looked for differential effect in terms of improved event-free survival, response rates or overall survival. Some have shown improved effectiveness with different dose scheduling, for example superior paclitaxel effect was seen in some studies comparing weekly scheduling with three weekly scheduling in both breast cancer (126) and ovarian cancer (127). These studies were not however conclusive and clear evidence of differential toxicity is uncertain. This is an area which is evaluated in depth in chapter 2.

1.3 ASSESSMENT AND GRADING OF SEVERITY OF CIPN

There is no standardised approach to the assessment of chemotherapy induced peripheral neuropathy. It is a subjective adverse effect and this makes assessment and grading particularly challenging. It is very difficult to compare CIPN outcomes between studies and treatment regimens due to the variability of assessment and grading tools used. One systematic review in non-small cell lung cancer patients identified 14 studies

reporting CIPN and within these, 11 different tools were used to categorise severity (128).

Objective measures of neuronal damage exist, and such neurophysiological measures include nerve conduction studies which give a quantification of sensory or motor nerve action potentials, respectively. The amplitude of these sensory action potentials may be reduced in CIPN reflecting axonal loss. Nerve conduction studies are a truly objective measure of nerve damage and can be considered a gold standard of measurement of neurotoxicity. However, they are not without their pitfalls. Firstly, they can be uncomfortable. Some studies have suggested that a reduction in sensory nerve action potentials in the sural nerve at mid-treatment may be predictive of more severe neuropathy (99, 129). By contrast, other studies have not shown sensory action potentials to be helpful in predicting outcome (130), and conversely it has been shown that they may not reflect nerve damage until late in the development of symptoms (131, 132). Results of testing also don't necessarily correlate with severity of symptoms (133). NCS will give more of a picture of large fibre damage and may underestimate small fibre damage which may result in significant neuropathic pain without objective evidence of neurotoxicity (134). Additionally, Argyriou et al noted that whilst electrophysiological measurements improved following chemotherapy, there was no correlation with patient self-reports of persistent symptoms (135). NCS have a role in excluding other forms of neuropathy if there is a reason for diagnostic doubt as to the aetiology of neuropathy.

Electromyography is not routinely helpful. It gives a non-quantitative assessment of harm to motor units where there is significant motor impairment, which is less useful in this predominantly sensory neuropathy and can be measured clinically without distress and discomfort to the patient (136). Some groups have used quantitative sensory threshold testing (QST). This assesses the threshold for sensory stimuli, such as vibration or thermal sensation, and again may objectively measure sensory disturbance. However standardisation of the methods and instruments does not exist (136).

Measures that involve neurological examination have shown to have advantages. There is some evidence that certain clinical neurological findings may correlate well with nerve conduction study findings (137). However whilst some studies suggest that inter-

and intra-observer reliability may be good (138), other studies suggest the contrary (133).

Some scales incorporate a few of the above neurophysiological measures and neurological examination to result in a final score or grading but most use a descriptive scale alone with a score assigned of 0-3 or 0-4, based on severity as judged by the clinician along with assessment of impact on various functions or activities of daily living. The most widely used assessment measure is the National Cancer Institute Common Toxicity Criteria for Adverse Events (NCI CTCAE) toxicity grading scale (139). However, inter-observer variation has been reported to be high with just under 50% of agreement between different assessors (140). This improves with training. Table 1.1 summarises this scale along with others in common use including the World Health Organisation (WHO) scale (141), Ajani scale, Eastern Cooperative Oncology Group (ECOG) scale (142), Oxaliplatin Specific Scale (143) and the Total Neuropathy Score (144). The Total neuropathy score (TNS) is a tool originally validated in diabetic peripheral neuropathy (145) but has been well studied in oncology populations. It is significantly correlated with the NCI CTC scale but is felt to have superior responsiveness to change over time as a score out of 40 is given rather than being limited to only four or five categories (146). It adds some objectivity in both sensory testing but also for motor neuropathy assessment where there is a suggestion that NCI CTC grading could in fact overestimate the severity of the effect as it fails to differentiate accurately between weakness due to motor nerve damage as opposed to cachexia or fatigue (147).

The disadvantage of this composite tool is the in-depth nature of the evaluation requiring clinical examination and NCS to complete it along with additional time and equipment. Revised and modified versions of the total neuropathy score have been developed and shown to correlate with full TNS scores but easier to perform in routine clinical practice (146, 148). The various versions of the total neuropathy score also have practical pitfalls because neurological examination is required in all patients and there may also be problems with inter-examiner variability particularly when this may be performed by oncologists or research nurse practitioners, rather than neurologists as was the case in some of the studies (149).

Table 1.1. A summary of the different grading scales in use for CIPN

Grading scale		Grade 0	Grade 1	Grade 2	Grade 3	Grade 4
NCI CTC (version 4)(139)		Normal	loss of deep tendon reflexes or paraesthesia (including tingling) but not interfering with function	objective sensory loss or paraesthesia (including tingling), interfering with function, but not interfering with activities of daily living	sensory loss or paraesthesia interfering with activities of daily living	permanent sensory loss that interferes with function
ECOG (142)		None or no change	Decreased deep tendon reflexes, mild paraesthesia	Mild or moderate objective sensory loss; moderate paraesthesia	Severe objective sensory loss that interferes with function	-
WHO(141)		None	Paraesthesia and/or decreased tendon reflexes	Severe paraesthesia and/or mild weakness	Intolerable paraesthesia and/or marked motor loss	Paralysis
Ajani scale (150)		Normal	Paraesthesia, decreased deep tendon reflexes	Mild objective abnormality, absence of deep tendon reflexes, mild to moderate functional abnormality	Severe paraesthesia, moderate objective abnormalities, severe functional abnormalities	Complete sensory loss, loss of function
Total neuropathy score	Sensory symptoms	None	Symptoms limited to fingers or toes	Symptoms extend to the ankle or wrist	Symptoms extend to knee or elbow	Symptoms above knees or elbows or functionally disabling
	Motor symptoms	None	Slight difficulty	Moderate difficulty	Requires help/ assistance	Paralysis
	Autonomic symptoms	0	1	2	3	4 or 5
	Pin sensibility	Normal	Reduced in fingers/toes	Reduced to wrist/ankle	Reduced to elbow/knee	Reduced to above knee/elbow
	Vibration sensibility	Normal	Reduced in fingers/toes	Reduced to wrist/ankle	Reduced to elbow/knee	Reduced to above knee/elbow
	Strength	Normal	Mild Weakness	Moderate Weakness	Severe Weakness	Paralysis
	Deep tendon reflexes	Normal	Ankle reflex reduced	Ankle reflex absent	Ankle reflex absent, others reduced	All reflexes absent
	Sural amplitude	Normal/reduced by <5% LLN	76-95% LLN	51-75% LLN	26-50% LLN	0-25% LLN

	Peroneal amplitude	Normal/reduced by <5% LLN	76-95% LLN	51-75% LLN	26-50% LLN	0-25% LLN
	Vibration sensation	Normal-125% ULN	126-150% ULN	151-200% ULN	201-300% ULN	>300% ULN
Oxaliplatin specific scale (136, 143)		No paraesthe-sia	Paraesthesia of short duration (<7 days)	Paraesthesia lasting 8-14 days	Paraesthesia persisting in the intercycle period	Paraesthesia causing functional impairment

Table 1.2. Different forms of the Total Neuropathy Score

Variable	TNS	TNSr	mTNS	TNSc
Pin prick	Yes	Yes	Yes	Yes
Vibration threshold testing via tuning fork	Yes	Yes	-	Yes
Vibration testing via QST	Yes	-	Yes	-
Thermal threshold via QST	Yes (in the original version)	-	-	-
NCS-sensory	Yes	Yes	-	-
NCS- motor	Yes	Yes	-	-
Deep tendon reflexes	Yes	Yes	Yes	Yes
Strength	Yes	Yes	Yes	Yes
Subjective report Sensory Motor Autonomic (fainting, impotence, constipation, loss of bladder and bowel control)	 Yes Yes Yes (in original)	 Yes - -	 Yes Yes -	 Yes - Yes

Adapted from Lavoie Smith(149)

All scales that have been used are relatively insensitive for mild neuropathy; for instance, if neuropathy isn't interfering with any functions it may be scored at a very low level even though the sensory symptoms may cause discomfort and distress to patients. This then brings the argument for patient-reported aspects to assessment and modules for this purpose have been developed.

Patient reported outcome tools and quality of life modules

The Functional Assessment of Chronic Illness Therapy (FACIT) measurement system comprises a large collection of health-related quality of life questionnaires tailored to a

variety of aspects of chronic illness (151). The system first started out with the FACT (Functional assessment of Cancer Therapy) questionnaires. Some are disease specific, whereas some are designed for specific symptoms or adverse drug effects. The FACT-taxane module is a taxane-specific subscale which has been validated and psychometric testing has supported its use for measuring the adverse effects of taxane therapy (152). Part of this module includes a neurotoxicity component (Ntx) which comprises 11 questions related to symptoms such as tingling, discomfort, cramps and hearing problems as well as functional questions such as those related to trouble with buttoning shirts and walking. This was validated separately as the FACT/Gynecology Oncology Group (GOG)- NTx (153). A peripheral neuropathy questionnaire (PNQ) developed and tested in oncology practice consists of two sections, one for patients to assess the severity of sensory symptoms and one to assess severity of weakness with descriptors to guide patients to select the most appropriate level for their symptoms. It also includes a section for patients to report activities which may be affected by their symptoms. In testing it was found that this questionnaire had higher levels of sensitivity compared to the FACT- GOG- Ntx and NCI CTC and good responsiveness to change over time (154). The European Organisation for Research and Treatment of Cancer (EORTC) has also developed a chemotherapy-induced peripheral neuropathy module for use alongside its general EORTC QLQ C30 quality of life scale (155). This includes 20 questions and has been validated and tested in several different languages and shows good levels of responsiveness to change over time (136, 156). Evidence suggests that the QLQ-CIPN20 may be better than the NCI CTC scale in detecting the effect of sensory symptoms (136). Neither the TNSc nor NCI-CTC scales have a perfect relationship with patients' reports using the EORTC-C30 and CIPN20 modules. Most of the discrepancies lie in the intermediate grades of severity (157). This is to be expected as one would hope that patient reported data would bring out more important subjective detail compared to physician-directed tools.

There is clearly no standard measure for chemotherapy induced peripheral neuropathy but consensus is that any physician-directed measure should ideally be combined with a patient reported outcome measure (136).

1.4 PROPHYLAXIS AND TREATMENT OF CIPN

Calcium and magnesium infused around administration of oxaliplatin is one of the most commonly studied potential preventative measures. A meta-analysis performed in 2013 included three retrospective studies and four prospective randomised controlled trials and suggested a reduction in $\geq$ grade 2 chronic neuropathy (158-161), reduction in acute neurotoxicity (158, 159, 162) and higher delivered cumulative dose in the Ca/Mg infusion groups (158, 159, 163). However there was some concern of bias given the large proportion of patients from retrospective studies and the lack of benefit seen by some prospective studies (162, 164), albeit these may be underpowered due to early closure (158). The reason for this was that alarm was raised regarding a possible deleterious effect on anti-tumour efficacy with the Ca/Mg infusions alongside chemotherapy (165). However in a subsequent study, this was not been confirmed and in fact there has been no proven difference in response rate or survival outcomes (158). A large, adequately-powered phase III double blind, placebo controlled study published has now shown no benefit of Mg/Ca^{2+} infusions in oxaliplatin-treated patients (166).
Vitamin E had been considered a potential preventative agent based on small studies (167); however a randomised, double- blind, placebo-controlled trial showed no evidence of benefit in platinum- or taxane- treated patients (168).
Glutathione has been studied as a potential preventative agent as it is an anti-oxidant agent which can reduce accumulation of platinum within the dorsal root ganglion (169). Some studies have shown some benefit (170, 171); however a randomised placebo controlled trial in patients treated with taxane/ platinum chemotherapy showed no difference in CIPN symptoms (172) with glutathione. N-acetyl cysteine has been studied based on belief that it may increase glutathione production but only 14 patients with oxaliplatin were involved and whilst there was a reduction in neuropathy in the treated group, such a small study has major limitations (173). Amifostine has been studied in several studies with some positive results (174, 175) but these have been inconsistent, of small magnitude when present and counterbalanced by adverse effects of its own (176).
Other postulated preventative therapies have been explored in generally small studies. For some therapies there was no significant difference seen such as with alpha-lipoic

acid (177), carbamazepine (178), amitriptyline (179) and recombinant human leukaemia inhibitory factor (180). In some studies there has been suggestion of benefit, for example for venlafaxine (181), omega- 3- fatty acids (182) and oxcarbazepine (183), but further data is required in order to draw final conclusions. Others have shown the intervention to be worse; for example in the case of nimodipine (184) and possibly acetyl-L-carnitine (185). With such protective strategies there is always some concern that there may be an impact on the anti-tumour effect of the drug.
The studies that are available are generally too small and heterogenous to draw definitive conclusions and there is insufficient evidence to suggest any treatment for the prevention of CIPN (118, 176)

Once peripheral neuropathy has developed it is difficult to treat. Neuropathic agents such as amitriptyline, gabapentin and pregabalin are frequently tried in clinical practice for symptom relief but trials of these agents have failed to show evidence of benefit (179, 186, 187). Lamotrigine has similarly been studied without benefit (188). Potential small benefits of nortriptyline have been noted but the study included only 51 patients (189).
Acetyl-L-carnitine has been the subject of trials in CIPN due to evidence pointing to benefits in expression of nerve growth factor, tubulin strength and improvement in sensory nerve conduction (190). There has been evidence of benefit in the therapy setting but caution exists due to potential harmful effects in the preventative setting and more evidence is needed before this may be considered an option (176, 190).
Topical treatments have also been studied. A ketamine and amitriptyline preparation showed no benefit (191) and a trend, but no significant benefit, was seen for a baclofen, ketamine and amitriptyline cream in patients with neuropathy largely due to taxane or platinum chemotherapy (192). There is insufficient evidence to recommend one specific treatment over another, but the most promising evidence so far has come from a study of duloxetine. A randomised double-blind, placebo-controlled trial of duloxetine was conducted including 231 patients treated with neurotoxic chemotherapy with at least NCI CTC grade 1 CIPN and an average pain score of at least 4 out of 10 using the Brief Pain Inventory-Short form. The results showed that there was a significant decrease in average pain score with 59% of those receiving the active

drug experiencing a decrease in pain compared with 38% of those receiving placebo. There was also an increased reduction in the reported numbness and tingling symptoms in those receiving duloxetine (193). Duloxetine is perhaps more effective in oxaliplatin-induced peripheral neuropathy than taxane-related neuropathy as suggested by subgroup analysis (193).

1.5 PHARMACOGENETICS AND ITS ROLE IN CLINICAL PRACTICE

Routine testing for single nucleotide polymorphisms (SNPs) associated with drug related adverse events is far from widespread, but its potential value to alter experience for patients is recognised. Some examples where genetic variants may contribute to different dosing requirements or occurrence of toxicity include the case of warfarin where it has been shown that two genetic factors along with body mass index can account for a significant proportion of variance in warfarin dose requirement and therefore also impact on bleeding risk (194). Certain variant alleles in the *thiopurine methyltransferase* (*TPMT)* gene have been correlated with different dosing requirements for thiopurines, such as azathioprine, mercaptopurine and thioguanine, to reduce the risk of myelosuppression(195). The presence of *CYP2C19*2* has been associated with resistance to the therapeutic effects of clopidogrel after primary coronary intervention (PCI) (196). Point- of-care testing for the variant allele has been prospectively studied to guide personalised treatment after PCI (197).

Many other examples exist, but very few pharmacogenetic variants are routinely tested for or mandated. The Food and Drug Administration (FDA) recommend *HLA-B*-15:02* testing prior to carbamazepine prescription due to an association between the variant allele and carbamazepine- induced Stevens-Johnson syndrome and toxic epidermal necrolysis, particularly in Asian patients, but uptake is variable (198). Some countries routinely carry out *DYPD* genotyping prior to fluorouracil based chemotherapy due to severe and potentially fatal toxicity (199, 200) that can ensue through administration to dihydropyrimidine dehydrogenase deficient individuals, but this is far from universal and is not carried in the UK.

The one example however where genotyping has become mandatory on a widespread basis is *HLA-B*57:01* testing prior to the prescription of the HIV-1 reverse transcriptase inhibitor, abacavir. Prior to testing approximately 5-8% of individuals receiving the drug would experience a hypersensitivity reaction with dermatological, gastrointestinal and respiratory consequences which were sometimes fatal. The variant was identified alongside two others initially and validated in other study cohorts (201, 202). The PREDICT-1 study was a randomised controlled study of prospective, pre-prescription testing and identified a negative predictive value of 100% (none of the patients in the screening group experienced immunologically confirmed hypersensitivity reactions) and positive predictive value of 47.9% (203). Introduction of routine screening has been shown to reduce the incidence of abacavir hypersensitivity from 8% to <1% (204). Situations where such a strong correlation to a single alleleic variant is identified are likely to be in the minority with more complex, multifactorial susceptibility patterns more common. However, it is clear that genotyping for variant alleles has the potential to form part of pre-prescription algorithms to more fully assess an individuals' sensitivity, likelihood of benefit and potential for significant adverse effects to lead to the ultimate aim of more personalised medicine.

1.6 AIMS OF THE THESIS

This introduction has outlined the problem of CIPN. It is a common adverse effect with the potential to be persistent after chemotherapy, impact on survivorship and there is no effective preventative measure or treatment. CIPN represents an adverse effect that warrants investigation to better define the most at risk groups. If one were able to better predict susceptible individuals it would aid more personalised counselling regarding the benefit/risk ratio of specific treatments. In some scenarios, where neurotoxic agents are utilised, for example oxaliplatin in adjuvant colorectal cancer therapy, or paclitaxel in addition to carboplatin in ovarian cancer, the absolute additional benefit conferred by the neurotoxic agent may be relatively small. In these situations, understanding the risks of long term toxicity and morbidity may have an

impact on the choice of treatment. A better understanding of the toxicity may also eventually lead to improved preventative or therapeutic strategies.

Three categories of risk factors will be explored in this work. Two are clinical risk factors: those related to features of the individual and those variables related to the treatment programme. The third is pharmacogenetic risk factors. These are related to single nucleotide polymorphisms (SNPs) in genes that may in some way affect the individual's reactions to the drug. Increasingly this is a focus of research and this work aims to review this systematically and contribute to the body of evidence. Finally, this project includes a quality of life assessment to explore objective evidence of long term impact of return to 'normal' after completion of chemotherapy. This will also aim to complement physician graded neuropathy in view of the problems with assessment and grading as discussed above.

CHAPTER 2

CLINICAL DETERMINANTS OF CHEMOTHERAPY INDUCED PERIPHERAL NEUROPATHY

2.1 INTRODUCTION

It is known that chemotherapy induced peripheral neuropathy affects a significant number of people who are treated with platinum agents, taxanes and vinca alkaloids. We have estimates of the proportion of patients affected from phase III clinical trials involving these agents. This chapter aims to evaluate the clinical factors that may influence risk of this adverse effect. Some of these factors were described in chapter 1 based on a narrative assessment of the literature. Such patient-related factors have been postulated to include age, gender, primary cancer, body mass index (BMI), ethnicity, alcohol consumption, diabetes and pre-existing neuropathy. Treatment-related factors include cumulative dose, schedule of drug delivery and duration of drug infusion. Many review articles cite these as potential factors affecting risk but there is little evaluation of the objective evidence for their influence on the development of CIPN. For a number of these factors, systematic review may be useful, but the feasibility of performing such review is challenging. Consideration of many of these clinical risk factors is frequently hidden in one or two sentences within large scale trials focusing on drug efficacy. Therefore, a broad-ranging systematic review of clinical risk factors was not considered feasible. The search terms that would have been necessary to identify all relevant studies were difficult to define and would have either risked missing many relevant articles or been so broad that screening the number of returned results would not have been achievable; age and gender are such examples.

Therefore, three factors were chosen for thorough systematic review to examine the evidence for a relationship with the development of CIPN and, where possible, meta-analysis was planned.

The three postulated risk factors were selected due to their clinical relevance and suitability for comparative studies, but also because it was possible to devise a specific search strategy and have confidence in the completeness of the review. The factors selected were

- the risk conferred by co-existing diabetes,
- the risk conferred by alcohol excess and
- the impact of drug scheduling on the development of CIPN.

Diabetes is associated with a risk of peripheral neuropathy with an estimated 13-23% of patients with type I diabetes and 24-33% of patients with type II diabetes developing the condition respectively (205, 206). It has therefore been considered that treating these patients with potentially neurotoxic drugs could interplay with their already, increased risk of developing peripheral neuropathy, albeit through different mechanisms. Excess alcohol is known to be associated with development of peripheral neuropathy likely through an interplay of direct toxic effects and nutritional complications (207, 208). It is therefore reasonable to speculate that it may have an effect on the susceptibility to CIPN. Scheduling of neurotoxic drugs, either in more or less dose- dense regimens has been postulated to affect toxicity, but evidence has been controversial. This chapter aims to provide a comprehensive overview of these factors and examine the evidence available.

2.2 METHODS

Systematic review methodology was used to explore the selected risk factors felt to be amenable to application of a search strategy which could be a) specific enough to identify a number of studies which would be able to be reviewed by a single investigator, but b) sensitive enough to identify relevant studies. Within each systematic review, where more than one comparable study existed for the same drug, using similar outcome definitions and appropriate methodology, meta-analysis was carried out to explore pooled effects in combined study samples. For each meta-analysis, inclusion criteria were set for each review and data were analysed. Forest plots were prepared using RevMan V5.0 (209) using the Mantel-Haenszel method, assuming a random effects model to allow for heterogeneity. The extent of heterogeneity between studies was estimated using the I^2 statistic and reasons examined where applicable.

2.2.1 Diabetes and association with development of CIPN

Systematic reviews were carried out using SCOPUS, Medline and Cinahl databases to investigate the potential effect of this factor on the risk of CIPN using the search strategy outlined below (table 2.1, 2.2 and 2.3). Full texts published studies in English were considered eligible if they investigated the risk of developing CIPN with potentially neurotoxic drugs in patients with a diagnosis of diabetes compared to the risk of developing CIPN in patients without a diagnosis of diabetes. The review was limited to the effects of neurotoxic cytotoxic chemotherapy drugs and did not include potentially neurotoxic novel targeted and biological agents. Both prospective and retrospective studies were included but in retrospective studies there needed to be evidence that the reported neuropathy occurred as a result of chemotherapy (for example, temporal evidence or case-note review of assessments during chemotherapy).

A standard data extraction form was utilised to collect information relating to patient demographics, treatment, primary cancer, measures of assessment and outcomes. Other confounding factors and methodological considerations were also considered along with the results of the studies.

Table 2.1. Search strategy for systematic review of diabetes and risk of CIPN

1.	Oxaliplatin
2.	Cisplatin
3.	Platinum
4.	Paclitaxel
5.	Docetaxel
6.	Taxane*
7.	Vincristine
8.	Vinca alkaloid
9.	Chemotherapy
10.	*sensory impairment*
11.	Neuropath*
12.	Neurotox*
13.	Diabet*
14.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
15.	10 OR 11 OR 12
16.	13 AND 14 AND 15

2.2.2 Alcohol and an association with CIPN

A search strategy was designed (table 2.2) to identify studies in the English language which compared the risk of developing peripheral neuropathy in patients who consumed alcohol or consumed alcohol to excess and those who did not. Studies focusing on biological or targeted agents rather than cytotoxic chemotherapy drugs were excluded. Both prospective and retrospective studies were included but in retrospective studies there needed to be evidence that the reported neuropathy occurred as a result of chemotherapy, for example, temporal evidence or case-note review of assessments during chemotherapy). The search strategy was applied to Medline, SCOPUS and Cinahl databases.

Table 2.2. Search strategy for systematic review of alcohol consumption and risk of CIPN

1.	Oxaliplatin
2.	Cisplatin
3.	Platinum
4.	Paclitaxel
5.	Docetaxel
6.	Taxane*
7.	Vincristine
8.	Vinca alkaloid
9.	Chemotherapy
10.	*sensory impairment*
11.	Neuropath*
12.	Neurotox*
13.	Alcohol*
14.	Ethanol
15.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
16.	10 OR 11 OR 12
17.	13 OR 14
18.	15 OR 16 OR 17

2.2.3 Scheduling of neurotoxic chemotherapy drug and association with CIPN

Finally, the search strategy for different schedules of drugs is detailed in table 2.3. The search was designed to explore neurotoxic drugs which are in common oncological practice. Ixabepilone and nab-paclitaxel were not specifically included in the search strategy as at the time of the search neither were in common use routinely in the UK. Some studies involving these drugs were identified so were mentioned in the results section.

Inclusion criteria were randomised controlled trials or other prospective comparative designs that reported differential rates of CIPN in groups receiving different schedules of the same potentially neurotoxic cytotoxic agent. Retrospective cohort studies were included provided there was evidence of prospective toxicity recording. Data extraction

was performed to allow collection of the key information regarding assessment and incidence of neuropathy but also purity of data in terms of acknowledgement and adjustment for confounding factors. Potential confounding factors were recorded, such as duration of infusion within each arm and total cumulative dose planned, as well as information regarding concurrent chemotherapy drugs. When considering planned cumulative dose, differences of >10% were noted.

Table 2.3 Search strategy for systematic review for scheduling of drug and risk of CIPN (Limited to controlled trials and articles in English).

1.	Oxaliplatin
2.	Cisplatin
3.	Platinum
4.	Paclitaxel
5.	Docetaxel
6.	Taxane*
7.	Vincristine
8.	Vinca alkaloid
9.	Neuropath*
10.	Neurotox*
11.	Schedule
12.	Dens*
13.	Weekly
14.	Frequency
15.	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8
16.	9 OR 10
17.	11 OR 12 OR 13 OR 14
18.	15 AND 16 AND 17

2.3 RESULTS

2.3.1 Diabetes and chemotherapy induced peripheral neuropathy

A total of 1034 articles matched the search criteria after removal of duplicates. This number included many articles not relevant to the risk of CIPN, but were more relevant to diabetes as articles on diabetic neuropathy were encompassed within the search strategy also. Of the total, 916 could be excluded based on their title. A further 97 articles were excluded after abstract review leaving 20 articles for full text review and inclusion (figure 2.1).

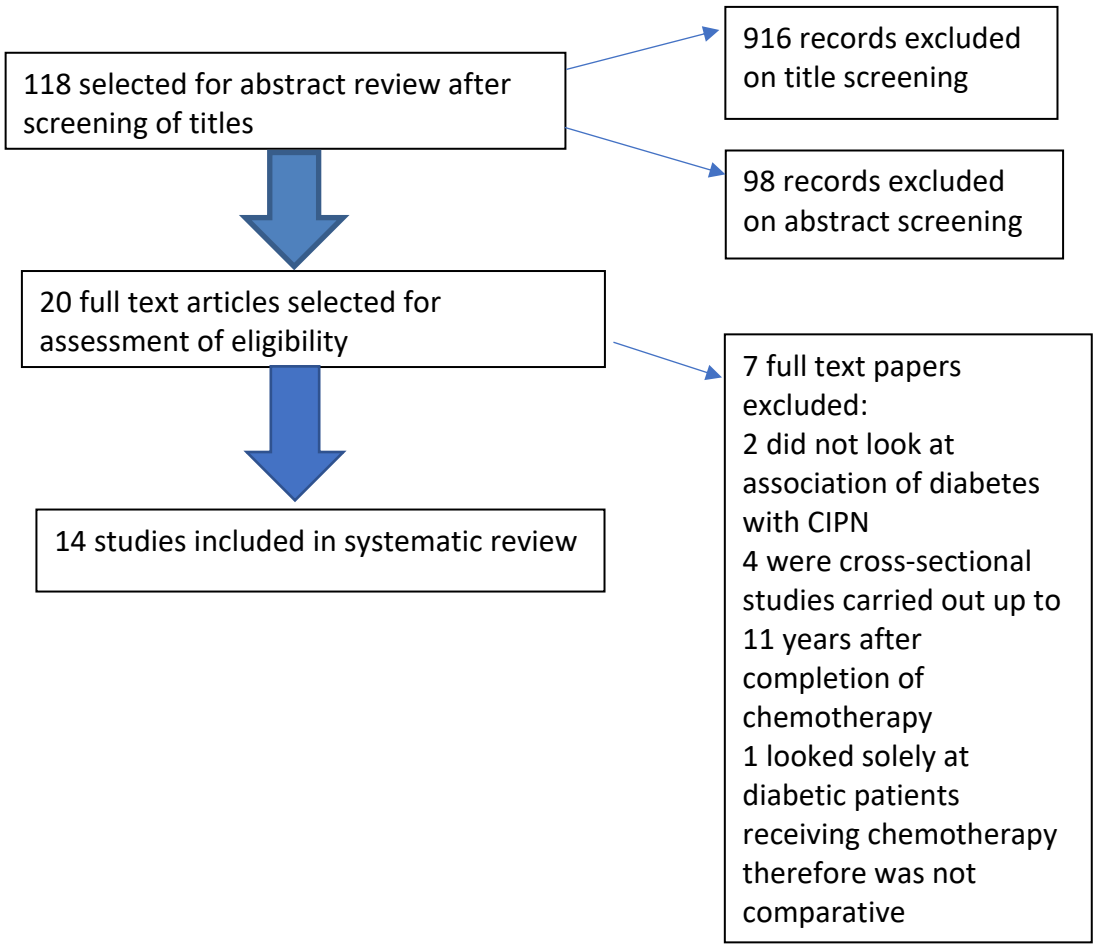


Figure 2.1 Flow diagram showing the numbers of studies identified for the systematic review of diabetes and risk of developing CIPN

Excluded studies

Seven studies were excluded; two did not look at association of diabetes with CIPN (210, 211) and one study looked solely at patients with diabetes receiving chemotherapy for ovarian cancer (212). Four studies did look for an association with diabetes but the assessment of neuropathy was usually >2 years after completion of chemotherapy. In one study, all patients were assessed >2 years after completion of oxaliplatin (10), while in the second, assessment was a mean of 6 years after chemotherapy (213). In the final two, assessment was at a median of 37 months (214), 41 months (cisplatin patients) and 18 months (oxaliplatin patients), respectively (215). In these four studies, there was no confirmation that the peripheral neuropathy started during or shortly after completion of chemotherapy.

Included studies

Fourteen studies were included (table 2.4). One study included four cohorts of patients treated with vincristine, taxanes, oxaliplatin and bortezomib. The bortezomib group was excluded from this analysis. These cohorts are treated separately for the purpose of our analysis. Mean sample size was 251 (range 45-1587) but this is skewed by one study with a very large group of 1587 patients treated with oxaliplatin (216). The median sample size was 123. Six studies involved oxaliplatin as the index neurotoxic drug (91, 93, 94, 97, 106, 216) and six studies focussed on an association with taxane induced neuropathy (76, 80, 84, 101, 103, 108). Kanbayashi et al, as mentioned above, included separate oxaliplatin, taxane and vincristine cohorts for analysis (78) and the final study looked at platinum neurotoxicity, but some of these patients also received a taxane drug (217).

Two studies were prospective in design (80, 106), while the remainder were retrospective cohort (78, 84, 91, 93, 94, 97, 101, 108, 216, 217) or case-control studies (76, 103).

Study findings

Seven of the studies demonstrated no significant effect of pre-existing diabetes upon the risk of developing CIPN (78, 80, 84, 97, 101, 103, 216). One of these studies demonstrated a trend towards increased risk in diabetic patients whilst showing a significantly increased risk with increased BMI (77). Two studies found an increased rate of CIPN in patients without a diagnosis of diabetes. The first showed a significant association between no diabetes diagnosis and development of NCI CTC grade $\geq$2 chronic oxaliplatin neuropathy which persisted on multivariate analysis (OR 14.1, 95%CI 1.3-166.7, p=0.03). This was a study of 85 Japanese patients all receiving oxaliplatin in the same dose and schedule (94). The second demonstrated an association with increased development of both acute and chronic oxaliplatin neuropathy in non-diabetic patients compared with diabetic patients which was seen in univariate analysis, but this was not seen when entered into a multivariate model (91).

The remaining five studies (76, 93, 106, 108, 217) demonstrated a significant association in the opposite direction, with diabetic patients experiencing more CIPN based on a number of outcome measures. A prospective cohort study involving 102 colorectal cancer patients receiving a standard schedule of adjuvant oxaliplatin demonstrated a markedly increased rate of NCI CTC grade 2 or greater chronic OIPN in those with diabetes, with 8 of 19 diabetic and 6 of 83 non-diabetic patients being affected (HR 4.86, 95%CI 1.16-21.50, p=0.03)(106).

De la Morena Barrio et al reported univariate analysis results of a significant increased in CIPN of any grade of both earlier onset and longer duration in patients with diabetes treated with paclitaxel. In their multivariate model, they demonstrated a higher risk of developing NCI CTC grade 2-3 CIPN in diabetic patients (OR 3.34, 95% CI 1.41-7.91, p=0.006) along with prolonged symptoms compared with non-diabetic patients (76).

Another study found no increased risk of developing CIPN in diabetic patients but those with diabetes who developed CIPN experienced this effect at a lower cumulative dose compared to those without diabetes (388mg/m^2 compared with 610mg/m^2) (93).

Johnson et al demonstrated an association with diabetes and increased development of any grade CIPN in platinum- treated lung cancer patients but this did not take into account that some patients received concurrent taxane whilst others did not, leading to potential confounding (217).

Kus et al showed no excess risk of developing CIPN in diabetic patients receiving a taxane with or without carboplatin. However, in a subgroup of patients who had had a diagnosis of diabetes for >5 years, there did appear to be an increased risk when compared to non-diabetic patients (OR 3.271, 95%CI 1.34-7.98, p=0.009) (108). It must however be noted, that whilst other clinical confounders were clearly considered, there is no evidence of formal adjustment for CIPN risk of receiving either paclitaxel or docetaxel or differing schedules of these drugs. The numbers of patients with or without diabetes in each of the different treatment groups however appeared to be well-matched.

Unfortunately, meta-analysis was not possible for this dataset. Either, patient numbers with and without diabetes, who did or did not suffer CIPN, were not provided (78, 94), the outcome evaluated was inconsistent with other studies (91, 101), the dose/ schedule was not provided to allow assessment of suitability for pooling of results (93), the treatment received by the patient cohort was too heterogeneous (80, 108, 215, 217) or, in the case of oxaliplatin studies, there was lack of clarity as to whether acute or chronic neuropathy was being assessed (97, 216).

Table 2.4. Summary of included papers for systematic review of effect of concurrent diabetes on risk of developing CIPN

Authors	Study design	Drug	Sample size	Number of patients with diabetes	Assessment tool used	CIPN outcome investigated	Were other patient-related variables accounted for	Were treatment-related variables looked for	Result with respect to effect of diabetes
Alejandro et al (91)	Retrospective	Oxaliplatin	50	6	'defined according to the oxaliplatin label'	Any acute or persistent neuropathy	Included patients with pre-existing PN and this along with age, gender, BMI and BSA went into multivariate analysis	Uniform treatment	Increased risk in non-DM patients on univariate analysis but this did not persist in multivariate analysis.
Bhatnagar et al (101)	Retrospective	Taxanes	123	20	Dose reduction due to CIPN	Dose reduction due to CIPN	Included patients with pre-existing PN. Included age, alcohol excess, race and gender in analysis	Either paclitaxel or docetaxel used and included in analysis.	No effect
De La Morena Barrio et al (76)	Retrospective case-control study	Paclitaxel	129	43	NCI CTC	Any CIPN, grade 2-3 CIPN, time to onset of CIPN and duration of CIPN	Excluded pre-existing neuropathy. Multivariate analysis including age	Uniform treatment Starting dose, total number of cycles included in multivariate analysis	Increased CIPN, grade 2-3 and delayed recovery in patients with DM
Eckhoff et al (103)	Retrospective case-control study	Docetaxel	150	6	NCI CTC	Grade 2-4 PN	Excluded pre-existing neuropathy. Included alcohol, age, BMI and PS in analysis	Two doses (75mg/m^2 and 100mg/m^2) included and adjusted for in analysis	Trend towards increased risk on univariate analysis but no significant effect.
Johnson et al (217)	Retrospective cohort	Platinum with or without taxane	735	85	NCI CTC	Any CIPN	Pre-existing PN allowed but none in the diabetic patients evaluated.	Type of platinum and whether or not taxane concurrently given was analysed but association with diabetes was univariate analysis and didn't include this	Increased risk with DM.
Kanbayashi et al (78)	Retrospective cohort	Taxanes Oxaliplatin Vincristine	58 52 52	5 6 4	NCI CTC	Any neuropathy	Excluded pre-existing PN. Age included in analysis	Did not account for different taxanes and slightly variable doses. Some taxane patients also received cisplatin concurrently Uniform treatment for oxaliplatin patients Vincristine doses and schedules were variable	No effect
Kus (108)	Retrospective cohort	Taxanes with or without carboplatin Taxanes alone Taxanes with carboplatin	374 270 104	81 59 22	NCI CTC and Neuropathic Pain Symptom Inventory	Any grade and grade 2-3	Excluded pre-existing PN and alcohol excess Looked for association with age and gender	No adjustment for different taxanes or schedule	No effect of DM but significant increased risk for those with DM for <5 years
Oguri et al .(94)	Retrospective cohort	Oxaliplatin	70	14	NCI CTC	Any neuropathy	Excluded pre-existing neuropathy. Also looked for association with age and gender.	Treatment standardised	Increased risk in non-DM patients
Ottaianno et al (106)	Prospective cohort	Oxaliplatin	102	19	NCI CTC	Grade 2-3	Excluded pre-existing neuropathy	Treatment standardised	Increased risk in diabetic patients with a HR 4.86 (1.16-21.50, p=0.03)
Pereira et al (80)	Prospective cohort	Predominantly taxanes	296 (214 received a taxane)	20	NCI CTC and TNSc	Any neuropathy	Included patients with pre-existing neuropathy. Associations sought with alcohol, age, thyroid disease	Treatment regimen very variable. Not everyone received a commonly neurotoxic drug. Associations sought with different treatment schedules	No effect
Ramanathan et al (216)	Retrospective cohort	Oxaliplatin	1587	135	NCI CTC	Any neuropathy and grade 3 or higher (however no clear definition between acute and chronic PN made)	Included patients with up to grade 1 pre-existing PN.	Oxaliplatin given at standard schedule with or without 5fU/LV.	No effect

Tanabe (84)	Retrospective cohort	Paclitaxel	219	18	NCI CTC	Grade 2-3 but also time to neuropathy and duration of neuropathy	Only excluded those with pre-existing 'severe' neuropathy. Alcohol not mentioned	Associations sought with different treatment schedules	No effect
Uwah et al (93)	Retrospective cohort	Oxaliplatin	62	15	NCI CTC	Grade 2-3	Excluded pre-existing PN. Also looked at age and gender, not alcohol	Schedule not mentioned	No effect on risk but developed at lower cumulative dose in DM patients
Vincenzi et al (97)	Retrospective cohort	Oxaliplatin	169	29	NCI CTC	Grade 2-3 (but no clear definition between acute and chronic OIPN)	No evidence of consideration of pre-existing PN. Age, gender, alcohol and other clinical parameters investigated.	Uniform treatment schedule	No effect

DM= diabetic, non-DM = non- diabetic

2.3.2 Alcohol and chemotherapy induced peripheral neuropathy

361 studies were identified after removal of duplicates. 336 articles could be removed based on title alone, and a further 21 were excluded after abstract review. Nine of these 21 abstracts were clearly not relevant to the question being addressed, 11 were review articles and one was a case report. Six studies were examined in full, and two were excluded (figure 2.2).

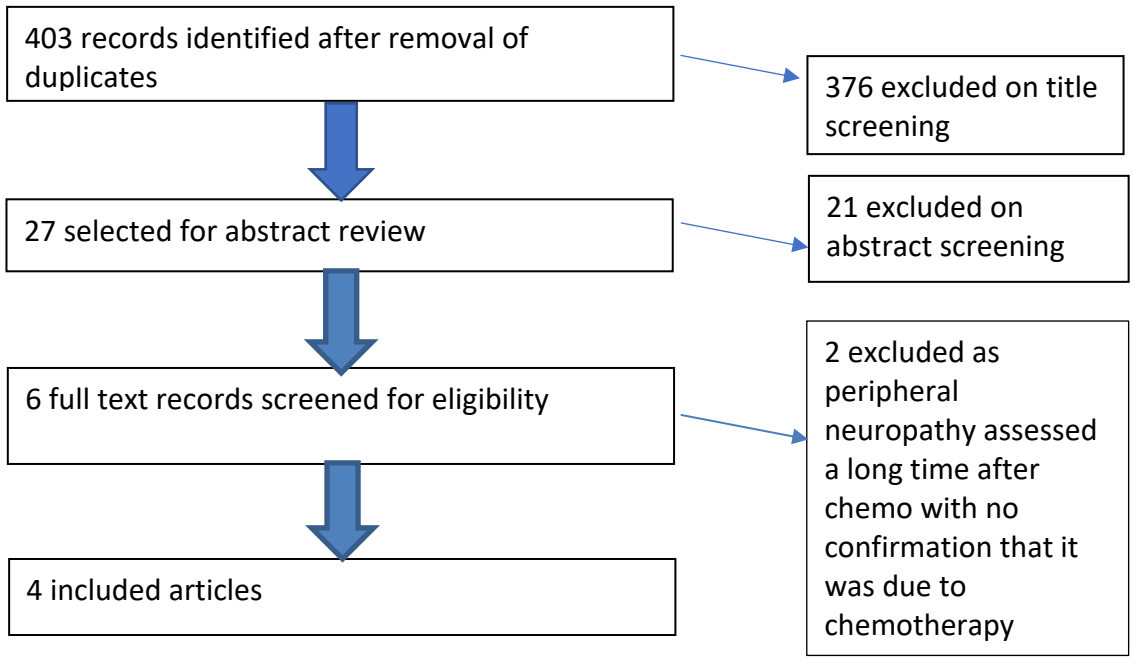


Figure 2.2. Flow diagram of identified studies for the systematic review of effect of alcohol consumption and risk of developing CIPN

Excluded studies

The first excluded study was designed to assess the risk factors for persistent neuropathy after oxaliplatin chemotherapy for colorectal cancer. Patients completed questions pertaining to sensory neuropathy from the Functional Assessment of Cancer Therapy/ Gynaecology Oncology Group- Neurotoxicity (FACT/GOG-Ntx) questionnaire at least 20 months from the last dose of oxaliplatin (median 37 months). They found a trend towards increased persistent neuropathy with regular alcohol consumption defined by more than 2 ‘standard’ drinks daily or more than 4 ‘standard’ drinks on a weekly basis. However, this study was not included in the systematic review due to the

fact there was no reference to assessment of neuropathy at the time of chemotherapy to confirm that peripheral neuropathy symptoms were oxaliplatin related. The second study performed vibration testing in 45 patients who had received either cisplatin or oxaliplatin at a median follow up of 46 and 18 months, respectively, without referral to assessments of neuropathy during or shortly after treatment and was therefore excluded for the same reason (215).

Included studies

The median sample size was 159.5 (range 33-296). The first was a prospective cohort study of women undergoing adjuvant or neoadjuvant chemotherapy for breast cancer (80). The second was a prospective study of patients undergoing oxaliplatin chemotherapy for hepatocellular carcinoma (218), and the third was a case-control study (12) of women receiving docetaxel for early breast cancer. The final study was a retrospective cohort study of patients who had undergone FOLFOX chemotherapy for colorectal cancer (97). The included studies are listed in table 2.7.

The smallest study, of 33 patients, investigated the combination of gemcitabine with oxaliplatin in the treatment of hepatocellular carcinoma. The study was designed and powered for its primary endpoint which was overall response rate. There was comparison of risk of neurotoxicity between those with alcoholic liver disease and those with non-alcohol related liver disease. In this study three patients developed grade 3 neurotoxicity as assessed by the oxaliplatin-specific scale, all were in the alcoholic liver disease group (3/25) with no grade 3 neurotoxicity in the non-alcoholic liver disease cohort (0/21), suggestive of increased risk, but the study size is the major limitation. Also, categorising risk according to alcoholic liver disease may not be widely applicable outside the field of hepatocellular carcinoma (218).

Vincenzi et al also noted an increased risk of developing CIPN in those patients who consumed alcohol (97). They recorded a rate of developing NCI CTC grade 2-3 CIPN of 69% in patients with a higher alcohol intake compared with 51% in patients with no excess alcohol intake according to their definition. A strength of this study is the

uniformity of treatment factors but the definition of alcohol excess is essentially one of binge drinking (≥ 5 glasses (men) or ≥4 glasses (women) in a single episode) rather than necessarily reflecting chronic alcohol consumption above accepted recommended limits in terms of unitary measurement.

Eckhoff et al (103) did not find an association with alcohol consumption ≥ 1 unit per week and development of NCI CTC grade 2-4 neuropathy compared with occurrence of grade 0-1 neuropathy (p=0.48). Similarly, Pereira et al did not find any association when they compared never drinkers to three categories of alcohol consumers: former drinkers, those who consumed ≤1 alcoholic drink per month and those who consumed >1 alcoholic drink per month (80). Both of these studies used very low levels of alcohol consumption in their investigations rather than looking at the risk of alcohol excess. This is a very different approach to those studies which found a statistically significant link with development of CIPN.

Due to the marked differences in study populations, outcome measures and risk categories used, meta-analysis was not feasible in this systematic review. The suggestion from the evidence available is that low levels of alcohol consumption do not appear to increase risk of CIPN, but alcohol taken to excess may possibly do so. However, again, no firm conclusions can be drawn due to the limited amount of data available.

Table 2.5. Table of included studies for the systematic review of association between alcohol consumption and CIPN

Paper	Study type	Drug	Sample size	Definition of alcohol excess	Numbers of pts according to alcohol intake	Grading tool for CIPN	CIPN outcome/s investigated	Were other patient related variables accounted for	Were treatment related variables accounted for	Result with respect to effect of alcohol
Eckhoff et al (103)	Case-control	Docetaxel	150	0 units/wk 1-14 units/wk >14 units/wk	24 118 8	NCI CTC	Grade 2-4 PN	Excluded pre-existing neuropathy. Included DM, age, BMI and PS in analysis	Two doses (75mg/m^2 and 100mg/m^2) included and included in analysis	No effect
Louafi et al (218)	Prospective	Oxaliplatin	33	Alcohol related liver disease (HCC trial)	13	Oxaliplatin specific scale	Grade 3	Excluded pre-existing PN. No other patient factors investigated	Standardised treatment	Increased risk of grade 3 neurotoxicity in alcohol-related liver disease (25% grade 3 vs 0%)
Pereira et al (80)	Prospective	Predominantly taxanes	296 (214 received a taxane)	Never drinkers Ex-drinkers < 1 standard drink per day >1 standard drink per day	12 2 52 15	NCI CTC and TNSc	Any neuropathy	Included patients with pre-existing neuropathy. Associations sought with DM, age, thyroid disease	Treatment regimen very variable Associations sought with different treatment schedules but not all patients received a commonly neurotoxic drug.	No effect
Vincenzi et al (97)	Retrospective	Oxaliplatin	169	5 or more glasses (men) or 4 or more glasses (women) in a single episode	13	NCI CTC	Grade 2-3	No evidence of consideration of pre-existing PN. Age, gender, DM and other clinical parameters investigated.	Uniform treatment schedule	Increased incidence with alcohol excess

2.3.3 Drug delivery and development of CIPN: Scheduling

This section covers delivering the neurotoxic drug in either less frequent, higher dose regimens or lower dose, more frequent, dose dense regimens. Figure 2.3 illustrates the flow of identified titles resulting in a collection of 49 articles that met the inclusion criteria. The 49 included studies were then sub-divided into drug specific group; paclitaxel, docetaxel, ixabepilone, oxaliplatin, cisplatin and vincristine for further evaluation.

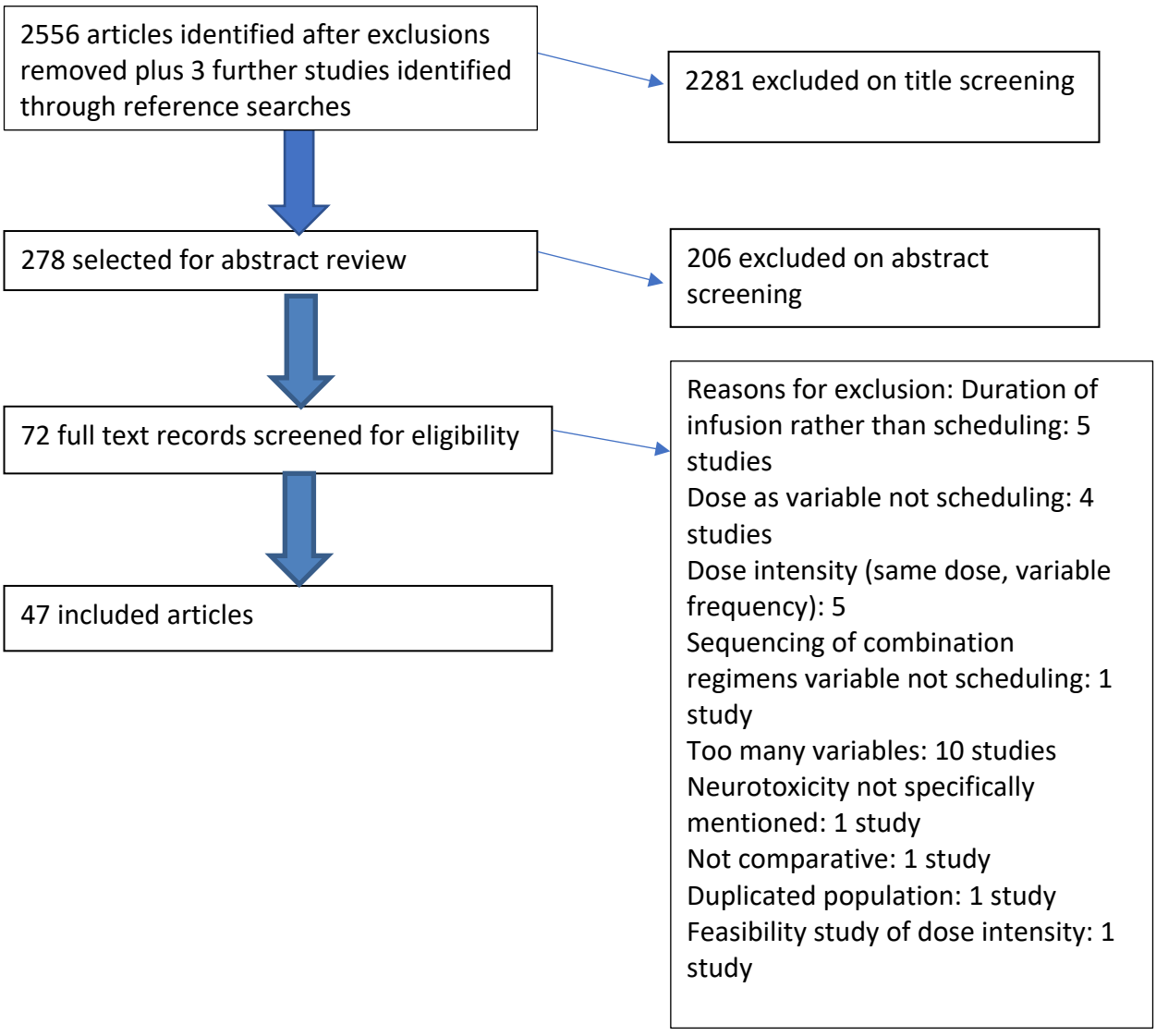


Figure 2.3. Flow diagram of identified studies for the systematic review of drug scheduling and risk of CIPN

Docetaxel

Included studies

There were 12 studies in total studying more versus less dose dense schedules of docetaxel. The median sample size was 108 (range 31-2466). For five of these studies, the primary outcome was a survival or response outcome (62, 126, 219-221). Five studies specifically listed toxicity as a primary outcome (222-226); for two of these their focus was on haematotoxicity (223, 224). The remaining two studies were primarily exploring quality of life outcomes (227).

Sample size and power calculations

In general, neurotoxicity was not a pre-specified primary outcome and therefore most studies did not justify their sample size for assessing neurotoxicity. No study specifically calculated study sample based on neurotoxicity. Two studies included a sample size calculation based on finding a difference in overall toxicity. The first based sample size on the ability to differentiate between an incidence of 30 and 60% of grade 3-4 toxicity but did not detail a power calculation (225). The second described a sample size and power calculation for detecting a difference in toxicity in general. However, it failed to meet its recruitment target of 160 patients and was therefore underpowered (226). The expectation therefore is that at least half of the included studies were underpowered to detect a clinically relevant difference in the development of CIPN.

Study type and randomisation

Eleven of the studies were prospective randomised controlled trials and one was a retrospective comparative study (221). Of the 11 randomised studies, seven described the method of randomisation (62, 219, 220, 225-228). Risk of randomisation bias overall was therefore considered to be low.

Potential patient- related confounding factors

Two studies excluded those with pre-existing peripheral neuropathy (220, 229), two excluded those with peripheral neuropathy equivalent to grade 2 severity or worse (62, 219) and one excluded those with greater than grade 2 neuropathy (228). No consideration was given to other potential predisposing factors such as concurrent diabetes, alcohol excess or BMI, albeit their effect on risk as discussed is not fully established. It is to be expected that this level of detail was not considered given the fact that neurotoxicity was not a key endpoint in the studies published. Only two studies were of first line chemotherapy with no patients receiving prior cytotoxic treatment (62, 228). In other studies patients may have been exposed to prior taxane or platinum treatment in the adjuvant setting or earlier palliative therapy. One study stratified its randomisation to account for previous taxane use (226) and one to account for previous platinum use (227). In the remainder of studies, a patients' previous exposure to neurotoxic chemotherapy may have been a confounding factor.

Potential treatment-related confounding factors

Treatment was generally well standardised and for the majority, the planned cumulative dose was similar in both arms (planned totals within 10% of each other). In two studies, the planned dose of docetaxel was higher in the more dose dense group, 720mg/m^2 versus 600mg/m^2 (224) and 840mg/m^2 versus 600mg/m^2 (223). In all but one study, docetaxel was given without any concurrent chemotherapy and, for the one that gave concurrent therapy, it was with doxorubicin which would not be envisaged to affect neurotoxicity (223). Most studies described a consistent duration of infusion, but in two studies was this not mentioned (220, 227). The studies are summarised in table 2.6.

Table 2.6. Included docetaxel studies for systematic review of dose dense versus less dose dense schedules and effect on risk of CIPN

Paper	Study type	Primary cancer	Sample size	Less dose-dense regimen	More dose-dense regimen	Any concurrent chemo	Grading tool	Frequency of CIPN (by grade)						Are patient factors considered	Are other treatment related factors considered	Difference
								Less dose dense			**More dose dense**					
								Any	**2-4**	**3-4**	**Any**	**2-4**	**3-4**			
Camps et al (219)	RCT	Lung	259	75mg/m^2 over 1h q21 until disease progression or unacceptable toxicity (n=129)	36mg/m^2 over 30m q7 (6 wks on, 2 off) until disease progression or unacceptable toxicity (n=125)	No	NCI CTC	43 (33)	-	1 (1)	47 (38)	-	4 (3)	Pre-existing PN grade $\geq$2 excluded.	All treatment standardised	No significant difference
Chen et al (220)	RCT	Lung	161	75mg/m^2 q21 for 8 cycles (n=33)	35mg/m2 days 1,8,15 q28 for 6 cycles (n=64) OR 40mg/m2 days 1 and 8 q21 for 8 cycles (n=64)	No	ECOG	2 (6)	-	0	11 (17) 5 (8)	- -	0 0	All pre-existing PN and neurological conditions excluded	All treatment standardised (except duration of infusion not stated)	No significant difference in grade 1-2
Gridelli et al (227)	RCT	Lung	114	75mg/m2 q21 for 6 cycles (n=106)	33.3mg/m2 weekly for 6 weeks then 2 week break for 2 cycles (n=108)	No	NCI CTC	19 (18)	7 (7)	0	20 (19)	7 (7)	2 (2)	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised (except duration of infusion not stated)	No SD between any grade neuropathy or grade 3-4
Lai et al (229)	RCT	Lung	50	66mg/m2 over 1h q21 for 9 cycles (n=25)	33mg/m2 over 1h days 1 and 8 q21 for 9 cycles (n=25)	No	NCI CTC	18 (72)	12 (48)	2 (8)	20 (80)	13 (52)	1 (4)	Pre-existing PN excluded	All treatment standardised	

Rivera et al (218)	RCT	Breast	118	75-100mg/m2 over 1h q21 until disease progression or unacceptable toxicity (n=59)	35-40mg/m2 over 30mins on days 1,8,15 q28 until disease progression or unacceptable toxicity (n=59)	Nil	NCI CTC	-	-	6 (10)	-	-	3 (5)	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised	
Shimazui et al (221)	Retrospective Comparative study	Prostate	31	70mg/m2 over 2h q21 until disease progression or unacceptable toxicity (n=16)	30mg/m2 over 2h days 1,8,15 q28 until disease progression or unacceptable toxicity (n=15)	No	NCI CTC	7 (44)	-	4 (25)	2 (13)	-	0	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised	Significantly more neuropathy in q21 group
Sparano et al (126)	RCT	Breast	2466	100mg/m2 over 1h for 4 cycles q21 (n=1236)	35mg/m2 over 1h q7 for 12 weeks (n=1230)	No	NS	-	197 (16)	49 (4)	-	197 (16)	74 (6)	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised	No significant difference
Stemmler et al (223)	RCT	Breast	85	75mg/m2 over 1 h q21 for 8 cycles (n=42)	35mg/m2 over 30m days 1,8,15 q28 for 8 cycles (n=43)	Adriamycin 50mg/m2 q21 or q28	NCI CTC	16 (38)	4 (10)	0	19 (44)	9 (21)	3 (7)	No exclusions for pre-existing PN. No other clinical factors mentioned	Higher planned cumulative dose in dose dense arm otherwise standard	
Stemmler et al (224)	RCT	Breast	102	75mg/m2 over 1h q21 for 8 cycles (n=54)	30mg/m2 over 30m days 1,8,15 q28 for 8 cycles (n=48)	No	NCI CTC	22 (41)	8 (15)	2 (4)	22 (46)	7 (15)	0	No exclusions for pre-existing PN. No other clinical factors mentioned	Higher planned cumulative dose in more dose dense arm otherwise standard	

Tabernero et al (225)	RCT	Breast	83	100mg/m2 q21 (42) until progression or unacceptable toxicity	40mg/m2 weekly for 6 weeks then 2 weeks off (n-41) until progression or unacceptable toxicity	No	NCI CTC	-	-	7 (17)	-	-	1 (2)	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised	3 weekly significantly more neurotoxic
Tannock et al (62)	RCT	Prostate	669	75mg/m^2 over 1h q21 for 10 cycles (n=335)	30mg/m2 over 30 mins weekly for 5 of every 6 weeks for 5 cycles (n=334)	No	NCI CTC	100 (30)	-	-	79 (24)	-	-	Pre-existing PN grade $\geq$2 excluded.	All treatment standardised	
Walker et al (228)	RCT	Breast	89	100mg/m2 over 1h q21 for 4 cycles (n=44)	33mg/m2 weekly for 12 cycles (n=45)	No	NCI CTC	16 (38)	-	-	0 (0)	0 (0)	0 (0)	Pre-existing PN grade >2 excluded	All treatment standardised	3 weekly significantly more neurotoxic

Meta-analysis

Given that CIPN outcomes were not the focus of most of the studies, the number of patients experiencing CIPN was not universally documented but where these were available, this data was entered into a meta-analysis. Nine studies presented suitable data for development of any grade of CIPN, and ten presented data for development of grade 3-4 CIPN. Nine of those included for the grade 3-4 neuropathy analysis used the NCI CTC grading scale. One study was excluded (220) as they used the ECOG toxicity grading scale. Whilst this is not a problem for the 'any CIPN' analysis, as CIPN is either present or not regardless of grading scale, this study was excluded for the grade 3-4 analysis as the definition of grades of the two grading scales was sufficiently different to make combining data inappropriate.

There was obvious heterogeneity between the studies. Different studies involved different tumour groups and each study chose slightly different doses for their more and less dose dense groups, respectively, ranging from 66mg/m^2 to 100mg/m^2 for the less dose dense groups and 30-40mg/m^2 for the more dose dense groups. Initially all studies described above were entered into the meta-analysis. One study included two dose dense arms to compare against their less dose dense arm (220). For the purposes of this meta-analysis, these two arms were combined in the more dose dense category as they were similar and equivalent to the different dose dense options included from different studies. Forest plots were prepared including studies that provided patient numbers developing any grade of CIPN and grade 3-4 CIPN, respectively

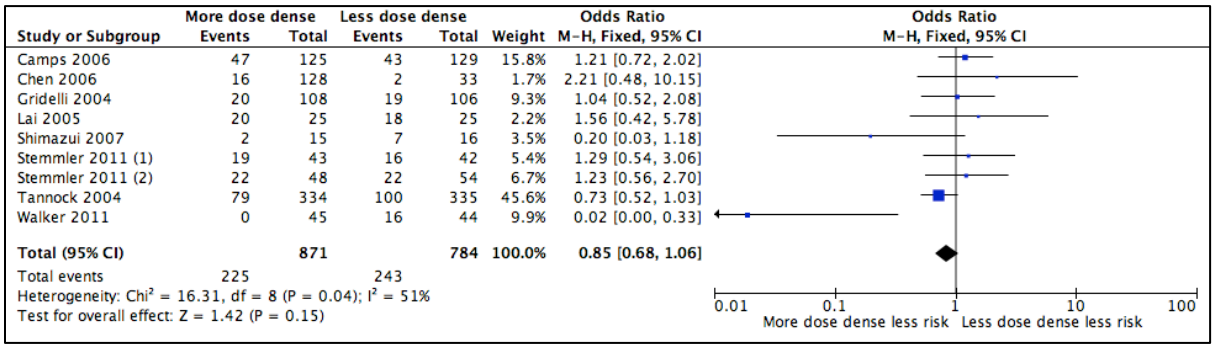


Figure 2.4. Forest plot demonstrating risk of developing any grade CIPN with more dose dense docetaxel regimens compared to less dose dense regimens

The analysis for development of 'any grade CIPN' (figure 2.4) suggests that weekly schedules are less neurotoxic than 3-weekly schedules, albeit not statistically significantly (OR 0.85, 95%CI 0.68-1.06, I^2=51%). This result is clearly skewed by one relatively small study of only 89 early breast cancer patients, by Walker et al (228), in which 36% of patients in the less dose dense group compared with no patients in the more dose dense group experiencing any grade CIPN. They used 100mg/m^2 in the less dose dense group which is at the top of the range used; however this is a commonly utilised, entirely reasonable dose. The more dose dense schedule involved a dose of 33mg/m^2. This dose was utilised by other studies within the analysis with substantially higher CIPN rates.

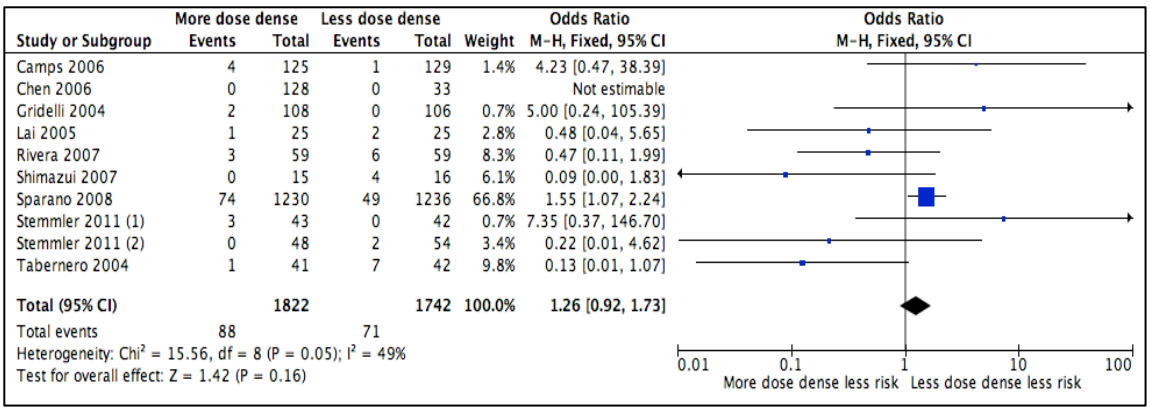


Figure 2.5. Forest plot demonstrating risk of development of NCI CTC grade 3-4 CIPN with more dose dense docetaxel regimens compared with less dose dense regimens

Nine of the twelve studies were included in the grade 3-4 analysis with a total of 3564 patients involved. Two studies did not give numbers of patients developing grade 3-4 CIPN (62, 228) and one used the ECOG grading scale (220). In the other two studies, numbers were not given. Notably, the trend in this analysis is in the opposite direction to the 'any grade' analysis (figure 2.5; OR 1.26, 95%CI 0.92-1.73, I^2=49%), but no statistically significant association is demonstrated. This result is particularly affected by the largest study included showing a statistically significantly higher risk of developing grade 3-4 CIPN in those receiving weekly docetaxel at a dose of 35mg/m^2 with an OR= 1.55 (95% CI 1.07-2.24). In this study, the three weekly dose was 100mg/m^2, at the top

end of the dose range, so their findings cannot be put down to this variable. The grade 3-4 meta-analysis does not include the Walker et al study which skewed the ‘any grade’ forest plot due to no patients developing neuropathy in their dose dense group which is out of keeping with the other studies.

Paclitaxel

Twenty-three studies were identified and are outlined in table 2.7.

Sample size and power calculations

The median sample size was 221 (range 27-2484). For all but three of the studies, outcomes related to development of CIPN were secondary endpoints or background data. Most studies focused on survival (126, 127, 230-237) or response (233, 238-242) outcomes. Only two studies were designed specifically to investigate the issue of comparative neurotoxicity of two paclitaxel regimens as their primary endpoint (84, 243). One was retrospective (84) and the other was a RCT which undertook sample size and power calculations for this specific purpose (243). This was the smallest of the included studies. A further retrospective study evaluated the incidence of CIPN that interfered with dose, and as part of this, compared the two paclitaxel regimens which patients received (3).

Study type and randomisation

Nineteen of these were randomized controlled trials and four were retrospective comparative studies. All four of the retrospective studies relied on review of medical documentation during chemotherapy to record toxicities (3, 84, 234, 244). Fourteen were multicentre studies (126, 127, 230-233, 235, 237-241, 245-247).
Eight studies described their method of randomisation or specified its nature as centrally and independently performed (127, 230, 231, 240-242, 247, 248).

Potential patient-related confounding factors

Four studies stated that patients with any pre-existing peripheral neuropathy were excluded from involvement (237, 238, 240, 243). A further study excluded those with greater or equal to grade 2 pre-existing neuropathy (241) and two excluded those with greater than WHO scale grade 2 neuropathy (239, 242). An additional study stated that

they excluded patients with 'severe neuropathy' (84). As development of CIPN was not a specified outcome for the majority of studies, it is unsurprising that pre-existing peripheral neuropathy was not accounted for more robustly. However, one of the studies that did specifically state neurotoxicity as its primary outcome stated that it excluded patients with pre-existing 'severe neuropathy' rather than 'any neuropathy' which appears somewhat unsatisfactory. This is a source of potential confounding outside of the four studies which excluded this factor completely.

Potential treatment-related confounding factors

Treatment was generally well standardised and for the majority the planned cumulative dose was similar in both arms (within 10% of total dose). In nine studies, however, the planned cumulative doses in the more dose dense groups were >10% greater than the planned cumulative doses in the less dose dense groups. In three of these, a cumulative dose of 1440mg/m^2 was planned in the more dose dense group compared with 1050mg/m^2 in the less dose dense group (84, 230, 234). A further two studies compared planned cumulative doses of 1440mg/m^2 in the more dose dense group against 1080mg/m^2 in the less dose dense group (127, 236) and an additional two studies compared planned cumulative doses of 960mg/m^2 in the more dose dense group versus 700mg/m^2 in the less dose dense group (3, 126). The final two of the nine studies involved planned cumulative doses of 1600mg/m^2 and 1200mg/m^2 (241), and 1200mg/m^2 and 900mg/m^2 (237), respectively.

For most studies, concurrent chemotherapy was consistent in both the more and less dose dense arms. In some studies in which carboplatin was the concurrent agent, the dose of carboplatin was also fractionated in the more dose dense paclitaxel arm (239, 246, 247). The effect of this on neurotoxicity is uncertain although carboplatin's neurotoxic potential is accepted as low. In one study, carboplatin was only given in the three-weekly paclitaxel arm and not the weekly cohort (231). Again, it is unlikely to make a big difference due to the very low rates of CIPN associated with carboplatin but, ideally of course, treatment should be standardised apart from the scheduling of the paclitaxel.

For six studies, duration of infusion was not stated and therefore confounding from unusually long or short infusions or inconsistency could not be assessed in these studies (84, 234, 237, 238, 244, 245). In the other studies, the infusion durations were those ordinarily used in clinical practice. It should be noted that one of the identified studies was a study of high dose chemotherapy with G-CSF support and therefore is not consistent with the others (240). This study was not considered suitable for inclusion in the meta-analysis due to the different treatment plan.

The studies were performed in patient cohorts being treated for breast cancer (3, 84, 126, 231-233, 240, 241, 245, 246), ovarian cancer (127, 230, 234, 236, 242, 247, 248) or lung cancer (235, 237-239, 243, 244).

Table 2.7. Included paclitaxel studies systematic review of dose dense versus less dose dense schedules and effect on risk of CIPN

Paper	Study type	Primary cancer	Sample size	Less frequent regimen (no. of patients)	Dose-dense regimen (no. of patients)	Any concurrent chemo	Grading tool	Frequency of CIPN (by grade)						Are patient factors considered	Are other treatment related factors considered	Difference
								Less dose-dense			**More dose-dense**					
								Any	**2-4**	**3-4**	**Any**	**2-4**	**3-4**			
Belani et al (237)	RCT	Lung	444	225mg/m2 q21 for 4 cycles (n=214)	100mg/m2 weekly on days 1,8,15 q28 for 4 cycles (n=217)	Carboplatin AUC6 q21 with 3 weekly paclitaxel and q28 with weekly paclitaxel	NCI CTC	-	39 (18)	-	-	26 (12)	-	Pre-existing neuropathy excluded	All treatment standardised although higher cumulative dose planned in dose-dense regimen	3-weekly significantly more neurotoxic Grade 2-3 neuropathy (18% vs 12%)
Budd et al (245)	RCT	Breast	2301	175mg/m2 q14 for 6 cycles (n=1162)	80mg/m2 weekly for 12 weeks (n=1139)	Nil	NCI CTC	-	-	201 (17)	-	-	119 (10)	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised	2- weekly more neurotoxic
Chan et al (230)	RCT	Ovarian	692	175mg/m^2 over 3 h q21 for 6 cycles (n=340)	80mg/m^2 over 1h weekly (Days 1,8,15, q21) 6 cycles (n=343)	Carboplatin AUC6	NCI CTC	254 (75)	61 (18)	7 (2)	233 (68)	88 (26)	9 (3)	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised although higher cumulative dose planned in dose dense regimen	Weekly more neurotoxic No difference in grade 3 neuropathy but significantly more grade 2-3 CIPN in weekly patients
Du et al (236)	RCT	Ovarian	221	180mg/m^2 over 3h q21 for 6 cycles (n=112)	80mg/m^2 over 1h days 1,8,15 q21 for 6 cycles (n=109)	Carboplatin AUC6	NS: any CIPN vs no CIPN	6 (5)	-	-	7 (6)	-	-	No exclusions for pre-existing PN. No other clinical factors mentioned	All treatment standardised although higher cumulative dose planned in dose dense regimen	No significant difference

Fountzilas et al (231)	RCT	Breast	416	175mg/m2 q21 for 6 cycles (n=131)	80mg/m2 weekly for 12 weeks (n=133)	Carboplatin with 3-weekly paclitaxel Nil with weekly paclitaxel	ECOG	-	-	7 (5)	-	-	11 (8)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	Carboplatin received by 3-weekly group only	Not statistically compared directly as there was a third (docetaxel-receiving) arm in the study
Green et al (232)	RCT	Breast	202*	225mg/m2 q21 for 4 cycles (n=127)	80mg/m2 weekly for 12 weeks (n=75)	Nil	NCI CTC	-	65 (51)	18 (14)	-	27 (36)	10 (13)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	All treatment standardised	Weekly less neurotoxic for grade 2-3 but note particularly high 3-weekly dose.
Ishii et al (243)	RCT	Lung	27	200mg/m^2 over 3h q21 (n=14)	100mg/m^2 over 1h on days 1 and 8 q21 (n=13)	Carboplatin AUC 6 or 3	NCI CTC	8 (57)	5 (36)	1 (7)	2 (15)	0	0	Both pre-existing PN and diabetes excluded	Not clear how many cycles planned/ received in each arm	Weekly significantly less neurotoxic
Katsumata et al (127)	RCT	Ovarian	631	180mg/m^2 over 3h q21 for 6 cycles (n=319)	80mg/m^2 over 1h weekly for 6 cycles (days 1,8,15 q21) (n=312)	Carboplatin AUC6	NCI CTC	-	-	20 (6)	-	-	21 (7)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	Treatment standardised although higher cumulative dose planned in dose dense arm and some patients in each arm received >6 cycles	No significant difference
Khoo et al (241)	RCT	Breast	139*	175mg/m^2 over 3h q21 for 8 cycles (n=72)	100mg/m^2 over 1h on days 1 and 8 q21 for 8 cycles (n=67)	Gemcitabine	NCI CTC	-	-	2 (3)	-	-	1 (1)	Excluded with pre-existing PN of grade 2 or greater or uncontrolled diabetes	Lower dose gemcitabine given in dose-dense arm (100mg/m^2 vs 1250mg/m^2) and higher cumulative dose planned in dose dense arm	No significant difference

Lalisang et al (240)	RCT	Breast	106	200mg/m^2 over 3h q21 for 6 cycles (n=51)	175mg/m^2 over 3h q10 for 6 cycles (n=55)	Epirubicin 110mg/m^2 q21 in the 3 weekly arm (dose-escalated) and epirubicin 75mg/m^2 q12 in the dose dense arm	NCI CTC	-	-	3 (6)	-	-	5 (9)	Excluded pre-existing neuropathy and prior taxane	Different epirubicin schedule although wouldn't be expected to altered neurotoxicity. Higher cumulative dose planned in less frequent schedule	
Perez et al (246)	Concurrent phase II trials	Breast	91	200mg/m^2 over 3h q21 for 8 cycles (n=43)	80mg/m^2 over 1h on days 1,8,15 q28 for 6 cycles (n=48)	Carboplatin AUC6 and trastuzumab for 3-weekly arm, carboplatin AUC2 and trastuzumab for weekly arm	NCI CTC	38 (88)	-	9 (21)	35 (73)	-	1 (2)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned. No prior platinum allowed	Standardised treatment. Carboplatin and trastuzumab fractionated in the weekly arm.	3- weekly more neurotoxic
Pignata et al (247)	RCT	Ovarian	799	175mg/m2 q21 for 6 cycles (n=400)	60mg/m2 weekly for 18 weeks (n=399)	Carboplatin AUC6 in less dose dense arm/ AUC2 in more dose-dense arm	NCI CTC	163 (41)	68 (17)	10 (2.5)	122 (31)	24 (6)	0	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	Standardised treatment, Carboplatin fractionated in weekly group	3-weekly significantly more neurotoxic
Rosenburg et al (242)	RCT	Ovarian	205	200mg/m2 q21 apparently until progression (n=101)	67mg/m2 q7 (days 1,7,15 of 21 day cycle) apparently until progression (n=104)	Nil	WHO	86 (85)	-	29 (29)	84 (81)	-	11 (11)	Pre-existing PN >grade 2 excluded. Pre-existing PN patients split equally between the groups.	Those in the weekly arm received more cycles of treatment (7 vs 5.7)	Weekly less neurotoxic ($p<0.001$)

Safra et al (234)	Retrospective study	Ovarian	400	175mg/m2 q21 for 6-8 cycles (n=267)	80mg/m2 days 1,8,15 q21 for 6-8 cycles (n=133)	Carboplatin AUC 6 in less dose-dense arm or AUC2 in weekly arm	NCI CTC	91 (34)	-	12 (4)	25 (20)	-	1 (1)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	Carboplatin fractionated and higher planned cumulative dose in weekly arm	Weekly less neurotoxic
Sakakibara et al (238)	RCT	Lung	82	200mg/m2 q21 for an unstated number of cycles (n=40)	70mg/m2 days 1,7,15 q21 for an unstated number of cycles (n=42)	Carboplatin AUC 6 q21	NCI CTC	-	17 (43)	10 (25)	-	5 (12)	0	Pre-existing PN and uncontrolled diabetes excluded	Standardised treatment except for duration but both groups received median of 3 cycles	Weekly less neurotoxic
Schuette et al (239)	RCT	Lung	883	200mg/m2 q21 for 6 cycles (n=449)	100mg/m2 weekly for 6 of 8 weeks for 2 cycles (n=434)	Carboplatin AUC6 3-weekly arm/ AUC2 weekly arm	NCI CTC	-	-	41 (9)	-	-	19 (4)	Pre-existing PN of >grade 2 excluded.	Standardised treatment. Fractionated carboplatin in the weekly arm	Weekly less neurotoxic
Seidman et al (233)	RCT	Breast	617**	175mg/m2 q21 until progression or limiting toxicity (n=383)	80mg/m2 q7 until progression or limiting toxicity (n=232)	Randomised to trastuzumab or not	NCI CTC	-	-	27 (12)	-	-	49 (21)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	Standardised treatment except some patients received trastuzumab as per randomisation	Weekly more neurotoxic
Shimizu et al (244)	Retrospective study	lung	167	200mg/m2 q21 for 6 cycles (n=94)	70mg/m2 days 1,8,15 q28 for 6 cycles (n=73)	Carboplatin AUC6 q21 or q28 in less dose-dense/ more dose-dense arms respectively	NCI CTC	-	17 (18)	8 (8.5)	-	0	0	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	Standardised treatment other than total length of cycle (including carboplatin)	Weekly less neurotoxic
Socinski et al (235)	RCT	Lung	155	225mg/m2 q21 for 4 cycles (n=78)	75mg/m2 days1,8,15 q21 for 4 cycles (n=77)	Carboplatin AUC6 q21	NS	-	15 (19)	3 (4)	-	10 (13)	2 (3)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	All treatment standardised	No significant difference

Sparano et al (126)	RCT	Breast	2484	175mg/m2 q21 for 4 cycles (n=1253)	80mg/m2 q7 for 12 weeks (n=1231)	Nil	NS	-	251 (20)	63 (5)	-	332 (27)	98 (8)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	All treatment standardised although higher planned cumulative dose in weekly arm	Grade 2-4 significantly worse in weekly Grade 2- 20% vs 27%
Speck et al (3)	Retros pective study	Breast	279	175mg/m^2 q14 for 4 cycles (n=230)	80mg/m^2 q7 for 12 cycles (n=49)	NS	Dose-limiting CIPN	-	-	-	-	-	-	Excluded pre-existing neuropathy. Collected data on race, BMI, diabetes and other comorbidities	Planned cumulative dose differs by >10% (more in weekly)	Dose limiting CIPN more common in weekly compared to biweekly (24.5 vs 14.4%
Tanabe et al (84)	Retros pective study	Breast	212	175mg/m2 q21 for 6 cycles (n=188)	80mg/m^2 on days 1,8,15 q21 for 6 cycles (n=24)	Nil	NCI CTC	-	-	-	-	-	-	'Severe' pre-existing PN excluded. Diabetes recorded with no evidence of effect on CIPN	All treatment standardised although higher planned cumulative dose in weekly arm	Trend towards weekly being less neurotoxic on univariate analysis but not seen in multivariate analysis
Wu	RCT	Ovarian	29	175mg/m2 monthly until progressive disease or limiting toxicity (n=15)	60mg/m2 q7 until progressive disease or limiting toxicity (n=14)	Carboplatin AUC 6 or AUC2	WHO	10 (67)	3 (20)	1 (6)	5 (36)	3 (21)	1 (7)	No exclusions for pre-existing neuropathy. No other clinical factors mentioned.	Standardised treatment. Fractionated carboplatin in weekly arm.	No significant difference

*Only 2 arms of this 3 arm study included for our purposes

**Initial weekly arm received 100mg/m^2 but this was amended due to unacceptable toxicity. The group that received the subsequent dose of 80mg/m^2 are included in this analysis

Meta-analysis

CIPN outcomes were not the focus of most of the studies so numbers of patients experiencing CIPN was not always documented but where these are available, they were entered into the meta-analysis.

Combining studies which provided numbers of patients for development of any grade CIPN results in a total population of 2455 paclitaxel-treated patients within eight different studies (figure 2.6). The overall pooled result suggests that more dose dense regimens were significantly less neurotoxic than less dose dense scheduling with an OR 0.62 (95% CI 0.51-0.74, I^2=18%). There are clearly differences between the studies limiting the validity of this result. Different doses of paclitaxel in each arm is the most important limiting factor, along with subtle differences in scheduling of the more dose dense arms. The range of doses span from 175mg/m^2 to 200mg/m^2 in the less dose dense arms and 60mg/m^2 to 100mg/m^2 in the more dose dense arms. If one were to include only studies within a very narrow dose range, for example 175-180mg/m^2 and 70-80mg/m^2, respectively, then the results are consistent with the weekly regimens resulting in less risk of neuropathy (OR 0.62 95%CI 0.44-0.87, I^2=22%).

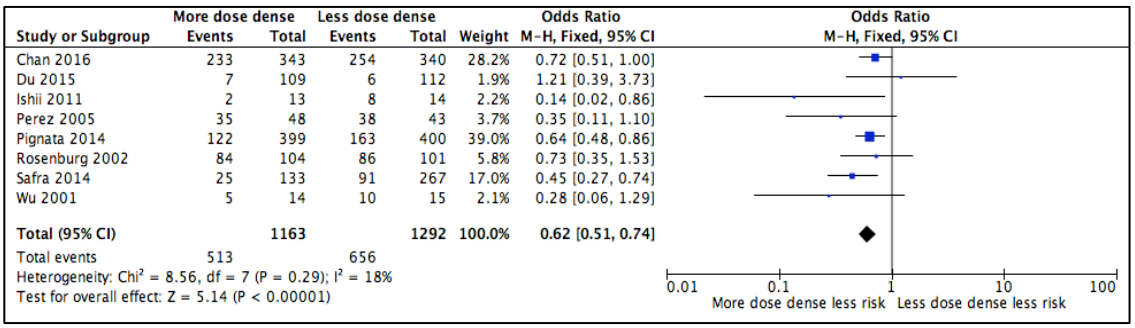


Figure 2.6. Forest plot demonstrating risk of development of any grade CIPN with more dose dense paclitaxel regimens compared with less dose dense regimens (all studies)

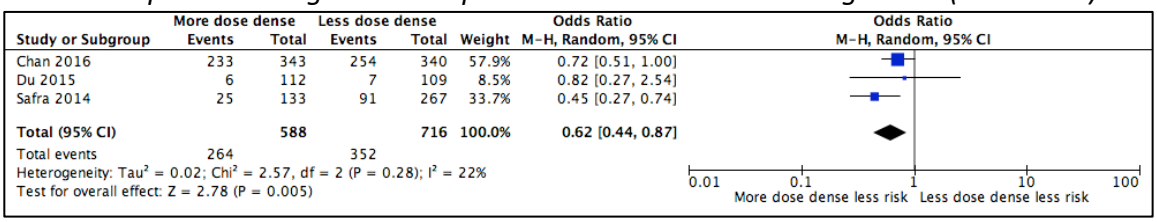


Figure 2.7. Forest plot demonstrating risk of development of any grade neuropathy and more dose dense paclitaxel regimens (selected dose range studies only)

Again, looking at pooled results for development of NCI CTC grade 3-4 neuropathy, this time of 9659 patients within 15 studies, the more dose dense arms appear to be less likely to cause NCI CTC grade 3-4 CIPN (figure 2.8; OR 0.65, 95% CI 0.38-1.11). Two studies report grade 3-4 neuropathy using the WHO scale (242, 248) and their outcomes are detailed in figure 2.9 showing a reduced risk of neuropathy with more dose dense schedules which is statistically significant (OR 0.32, 95%CI 0.15-0.67, I^2=0%). This is clearly heavily influenced by the larger Rosenberg study (242). A further study reported numbers of patients developing grade 3-4 neuropathy but used the ECOG scale (231). As this is the only study that used this assessment scale, it was excluded from meta-analysis.

As with the 'any grade' comparison, the main limiting factor was the different doses used in the more and less dose dense arms with ranges of 60-100mg/m^2 in the more dose dense and 175-225mg/m^2 in the less dose dense arms. If narrower inclusion criteria are applied and those using doses outside the most common dose ranges of 175-180mg/m^2 and 70-80mg/m^2 are excluded and only studies using the NCI CTC criteria are included, then the results look somewhat different and are less convincingly in favour of more dense regimens conferring lower neuropathy risk. (figure 2.10; OR 1.69, 95%CI 1.34-2.14, I^2=74%).

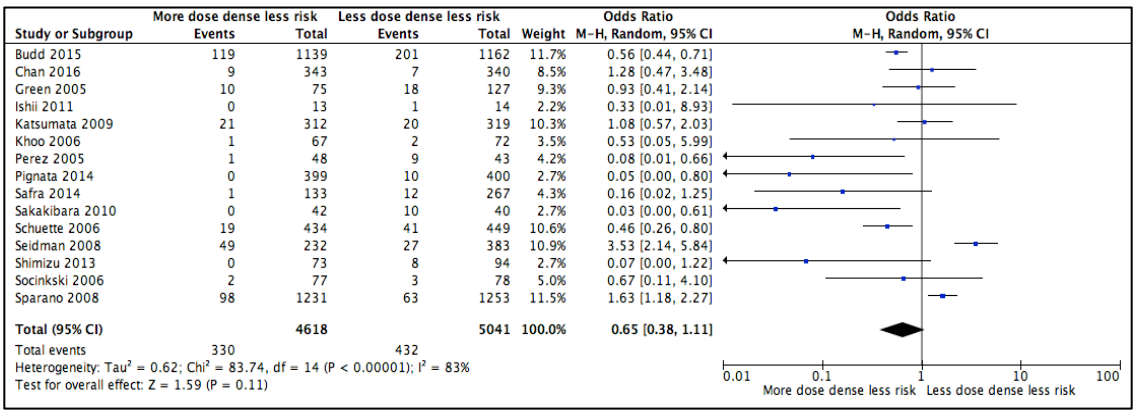


Figure 2.8. Forest plot demonstrating risk of development of NCI CTC grade 3-4 CIPN and more dose dense paclitaxel regimens dose dense paclitaxel regimens (all studies)

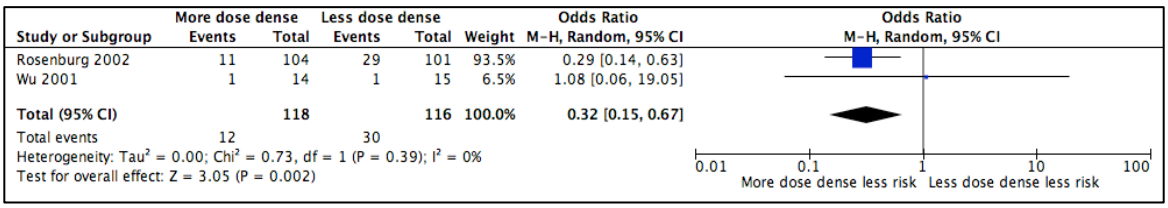


Figure 2.9. Forest plot demonstrating risk of development of WHO grade 3-4 CIPN with more dose dense paclitaxel regimens

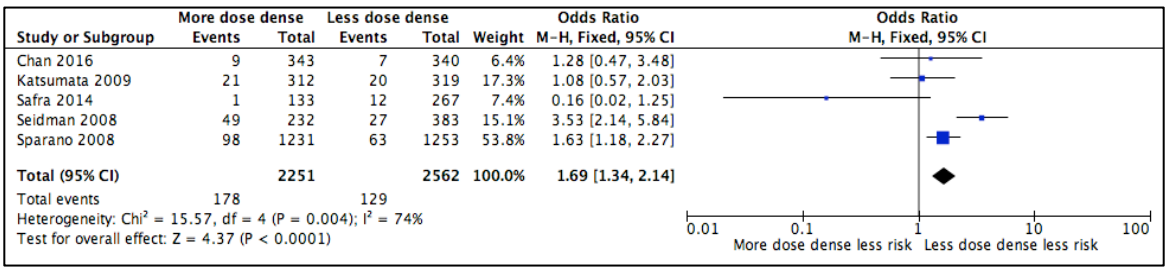


Figure 2.10. Forest plot demonstrating risk of development of NCI CTC grade 3-4 neuropathy with more dose dense paclitaxel regimens (selected doses range only)

Nab-paclitaxel

Two studies investigating different schedules of nab-paclitaxel were identified (table 2.8). One was a randomised controlled trial in 208 breast cancer patients comparing overall response rate and toxicity between three different dose schedules of the drug (249). The other study was a non-comparative randomised study comparing two schedules of nab-paclitaxel in lung cancer treatment. This study closed early due to slow recruitment and only 27 patients are included in the analysis (250). These were not entered into a meta-analysis as it was not known what grading scale had been used to assess neuropathy in either study, the results would have limited value with only two involved studies, particularly with the small sample size of one of the pair, and additionally, the regimens used were different between the two studies.

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Table 2.8. Included nab-paclitaxel studies for systematic review of dose dense versus less dose dense schedules and effect on risk of CIPN

Paper	Study type	Primary cancer	Sample size	Less frequent regimen (no. of patients)	Dose-dense regimen (no. of patients)	Any concurrent chemo	Grading tool	Frequency of CIPN (by grade)						Are patient factors considered	Are other treatment related factors considered	Difference
								Less dose dense			**More dose dense**					
								Any	**2-4**	**3-4**	**Any**	**2-4**	**3-4**			
Seidman et al (249)	RCT	Breast	208	260mg/m^2 q21 (n=75) until progression or unacceptable toxicity 260mg/m^2 q14 (n=54) until progression or unacceptable toxicity	130mg/m^2 q7 until progression or unacceptable toxicity	Bevacizumab	NS	66 (88) 48 (89)	-	25 (33) 30 (56)	66 (84)	-	36 (46)	Excluded pre-existing PN >grade 1	All treatment standardised apart from slightly differing bevacizumab schedule	No SD between 3-weekly and weekly arms
Grilley-Olson et al (250)	Non-comparative randomised trial	Lung	27	300mg/m^2 q21 (n=14)	100mg/m^2 q7 (n=13)	Carboplatin	NS			3 (21)			0	No prior chemo but no exclusions for pre-existing PN	All treatment standardised	Non-comparative

Cisplatin

For cisplatin, two studies, both randomised controlled trials, were identified and are outlined in table 2.9. One involved chemotherapy with concurrent radiotherapy for cervical cancer (251) and the other evaluated cisplatin schedule in the treatment of ovarian cancer (252). The sample sizes were 104 and 40, respectively. The larger of the two studies showed no significant difference between neurotoxicity rates. The smaller study was specifically designed to investigate neurotoxicity, but no sample size or power calculations were reported. They utilised various neurophysiological outcome measures in their study design and they reported significantly reduced sensory amplitude potentials in patients receiving the less dose dense regimen (cisplatin 75mg/m^2 q21) whilst they remained unchanged in those receiving cisplatin 50mg/m^2 on a weekly basis (252). These studies could not be combined in a meta-analysis due to the differences in neuropathy assessment scales utilised.

Table 2.9 Included cisplatin studies for systematic review of dose dense versus less dose dense schedules and effect on risk of CIPN

Paper	Study type	Primary cancer	Sample size	Less frequent regimen (no. of patients)	Dose-dense regimen (no. of patients)	Any concurrent chemo	Grading tool	Frequency of CIPN (by grade)						Are patient factors considered	Are other treatment related factors considered	Difference
								Less dose dense			**More dose dense**					
								Any	**2-4**	**3-4**	**Any**	**2-4**	**3-4**			
Cavaletti et al (252)	RCT	Ovarian	40*	75mg/m^2 q21 for 6 cycles (n=20)	50mg/m^2 q7 for 9 weeks	Nil	WHO Neurologic symptom score and neuropathy disability score. Sensory and motor nerve conduction studies ad somatosensory and visual evoked potentials	7 (37)	-	-	4 (21)	-	-	Any patients with conditions know to be associated with PN were excluded	All treatment standard	Significantly reduced sensory amplitude potentials in the less dose-dense group.
Ryu et al (251)	RCT	Cervix	104	75mg/m^2 over 1-2h q21 for 3 cycles (n=53)	40mg/m^2 over 1-2h q7 for 6 cycles (n=51)	Concurrent RT	NCI CTC	2 (4)	-	0	5 (10)	-	0	Previous chemo excluded otherwise clinical confounders not mentioned	All treatment standardised	No significant difference
Soto Parra et al (253)	RCT	Lung	107	70mg/m^2 over 30-60m q28 for 3-6 cycles (n=54)	70mg/m^2 over 30-60m q21 for 3-6 cycles (n=53)	Gemcitabine at different schedules	SWOG	-	-	1 (2)	-	-	0	No mention of clinical confounders	Concurrent gemcitabine differs but wouldn't be expected to alter neurotoxicity	No significant difference

*only 2/3 arms used for our purposes

Oxaliplatin

Seven studies were identified (table 2.10). Two were purely looking at schedule of oxaliplatin whereas five were comparing XELOX to FOLFOX regimens. Both sets of studies were included but this difference is considered.

The two purely oxaliplatin-scheduling studies compared oxaliplatin and capecitabine in a three-weekly to a two-weekly schedule. Both were randomised controlled trials, one involving 419 patients (254) and the other was smaller with a sample size of 89 patients (255). Both were designed to examine progression free survival and sample size and power calculations were reported for this outcome rather than neurotoxicity. Method of randomisation, and confirmation that this was centrally performed, was stated in both studies. The larger of the two studies stated pre-existing peripheral neuropathy as an exclusion factor whilst no such criteria were stated for the smaller study. Planned cumulative doses were similar and concurrent treatment in both studies was the same. This was with capecitabine with the doses differing between the two schedules as would be standard. For meta-analysis, the only outcome looked at was development of any grade CIPN as the two studies used different grading scales. One used NCI CTC (254) whereas the other used WHO (255) (Figure 2.11). Whilst it is reasonable to combine occurrence of any grade CIPN, the definition of grade 2, 3 and 4 neuropathy are sufficiently different to prohibit combination of these outcomes.

The largest of the five XELOX versus FOLFOX studies was a prospective randomised, two-arm, non-inferiority study comparing XELOX (oxaliplatin 130mg/m^2 on day 1 q21 followed by capecitabine 1000mg/m^2 orally twice daily on days 1-14) to FOLFOX4 (oxaliplatin 85mg/m^2 over 2h q14 with leucovorin 200mg/m^2 given on days 1 and 2 alongside a 5FU 400mg/m^2 bolus and 22 hour infusion of 5FU 600mg/m^2) (256). It became a 2x2 factorial study with further randomisation to bevacizumab or placebo; however for the purposes of this review the bevacizumab containing arm was excluded from neurotoxicity assessment. This still left 1307 patients with metastatic colorectal cancer who received either XELOX or FOLFOX4 without bevacizumab for assessment of neurotoxicity. The study was powered for progression-free survival assessment. No

exclusions were made for pre-existing neuropathy or other potential influencing factors for CIPN and there was no differentiation between acute and chronic OIPN. No significant difference was seen in sensory neurotoxicity rates between the two arms.

The second largest study (257), compared the same two oxaliplatin-containing chemotherapy regimens, again in patients with metastatic colorectal cancer. Again, the randomisation method was outlined, and the study was appropriately sized and powered for its primary endpoint which was progression-free survival. No exclusion factors that would have precluded patients with pre-existing neuropathy were mentioned. There was no differentiation of acute or chronic OIPN; however the rates of reported neurosensory toxicity were vastly lower than the Cassidy study (256). For example, the rate of any grade neuropathy in the FOLFOX-4 group was 17% in the Rothenberg study(257) versus 80% in the Cassidy study in both largely Caucasian study populations which both excluded any prior oxaliplatin therapy. This raises the suspicion, although it cannot be confirmed, that perhaps the Rothenberg study was reporting chronic OIPN whereas the Cassidy study may have been reporting combined acute and chronic toxicity. Similar to Cassidy et al however, the Rothenberg study did not show any difference in the incidence of neurosensory neuropathy.

The third randomised controlled trial comprised 306 patients and this time compared XELOX (as described above) with FOLFOX-6 (oxaliplatin 100mg/m^2 administered over 2 hours followed by leucovorin 400mg/m^2 and 5FU 400mg/m^2 as an IV bolus followed by 5FU 2400-3000mg/m^2 over 46 hours and repeated every 14 days) (258). Patients with a history of neuropathy were excluded. Randomisation process was described, and the study was designed and powered to meet its primary endpoint which was tumour response rate by central review. No differentiation was made between acute and chronic OIPN; however the rates of neurosensory toxicity (95% for FOLFOX6 and 90% for XELOX) suggest that both types of neurotoxicity were reported together. There was no significant difference in these rates of any grade of neuropathy, but a significantly higher rate of grade 3-4 OIPN was seen in the FOLFOX group (26% versus 11%, $p<0.001$).

All three of these randomised controlled studies stated that they used the NCI CTC grading scale for assessing toxicities. As the dose of oxaliplatin is different in the Ducreux study (258) this is a concern for inclusion in meta-analysis. The other two studies would be consistent enough in design and treatment strategy to be suitable; however there was real concern that the neuropathy outcome reported was different due to the notable difference in reported rates between studies.

The remaining two studies were both prospective, non-randomised studies (96, 259). The larger of these two studies used a modified FOLFOX regimen of oxaliplatin 85mg/m^2 over 2h q14 with leucovorin 200mg/m^2 given on days 1 and 2 alongside a 5FU 400mg/m^2 bolus and followed by a 46 hour infusion of 5FU 2400mg/m^2 (96). The primary outcome was incidence of severe neurotoxicity although no sample size or power calculation was described. The investigators looked for association between the regimen and an increased risk of developing severe CIPN as defined by grade 3-4 CIPN or grade 2 CIPN lasting for >7 days. This study was therefore not eligible for inclusion in meta-analysis due to this different outcome measure. They found a significantly increased risk of CIPN with the FOLFOX regimen with 39% of patients meeting the case definition compared to 19% in the three-weekly XELOX group ($p<0.01$ on uni- and multivariate analysis).

The final study in this category, another prospective non-randomised study of 150 chemo-naive colorectal cancer patients included patients treated with either FOLFOX4 or XELOX as described above. The aim of the study was to compare neurotoxicity rates between the two treatments. Patients with pre-existing PN, diabetes and alcohol excess were excluded. Cumulative doses were found to be similar in the two groups. Acute neurotoxicity was similar in both arms but there was a significantly increased incidence of chronic CIPN in patients treated with FOLFOX4 (64/77 versus 44/73 of XELOX patients experiencing at least grade 1 CIPN) (259).

Table 2.10. Included oxaliplatin studies for systematic review of dose dense versus less dose dense schedules and effect on risk of CIPN

Paper	Study type	Primary cancer	Sample size	Less frequent regimen (no. of patients)	Dose-dense regimen (no. of patients)	Any concurrent chemo	Grading tool	Frequency of CIPN (by grade)						Are patient factors considered	Are other treatment related factors considered	Difference
								Less dose dense			**More dose dense**					
								Any	**2-4**	**3-4**	**Any**	**2-4**	**3-4**			
Argyriou et al (259)	Prospective non-randomised study	CRC	150	130mg/m^2 q21 for 8 cycles (n=73)	85mg/m^2 over 2h q14 for 12 cycles (n=77)	Capecitabine as XELOX in 3-weekly treatment and 5FU/LV as FOLFOX for 2-weekly	NCI CTC (stated) and TNSc	44 (60)	43 (59)	9 (12.3)	64 (83)	45 (59)	8 (10)	Pre-existing PN, diabetes and alcohol excess were excluded.	XELOX versus FOLFOX rather than simply scheduling of oxaliplatin	FOLFOX (2 weekly) more neurotoxic than XELOX (3 weekly)
Baek et al (96)	Prospective non-randomised study	CRC	366	130mg/m^2 q21 until progression or unacceptable toxicity (n=79)	85mg/m^2 q14 until progression or unacceptable toxicity (max 12 cycles if adjuvant)(n=287)	Capecitabine as XELOX in 3-weekly treatment and 5FU/LV as FOLFOX for 2-weekly	NCI CTC	15 (19			111 (39)			Pre-existing PN excluded, various clinical factors considered	XELOX versus FOLFOX rather than simply scheduling of oxaliplatin	FOLFOX (2 weekly) more neurotoxic than XELOX (3 weekly)
Cassidy et al (256)	RCT	CRC	1307	130mg/m^2 q21 until progression or unacceptable toxicity (n=655)	85mg/m2 q14 until progression or unacceptable toxicity (n=648)	Capecitabine as XELOX in 3-weekly treatment and 5FU/LV as FOLFOX4 for 2-weekly	NCI CTC	534 (82)	-	114 (17)	515 (80)	-	107 (17)	No exclusion criteria related to pre-existing PN	XELOX versus FOLFOX rather than simply scheduling of oxaliplatin	No significant difference
Ducreux et al (258)	RCT	CRC	306	130mg/m^2 over 2h q21 for 8 cycles (n=156)	100mg/m^2 over 2h q14 for 12 cycles (n=150)	Capecitabine as XELOX in 3-weekly treatment and 5FU/LV as FOLFOX6 for 2-weekly	NCI CTC	139 (90)	-	17 (11)	141 (95)	-	38 (26)	Pre-existing PN excluded	XELOX versus FOLFOX rather than simply scheduling of oxaliplatin	Significantly less G3/4 PN with XELOX
Hurwitz et al (254)	RCT	CRC	419	130mg/m2 q21 until progression or unacceptable toxicity (n=208)	85mg/m2 q14 until progression or unacceptable toxicity (n=211)	Capecitabine at different doses per arm	NCI CTC	63 (30)	-	17 (8)	56 (27)	-	15 (7)	Pre-existing PN excluded. Other clinical confounders not mentioned	Different doses of capecitabine as is standard otherwise standardised	No significant difference reported for neuropathy and peripheral sensory neuropathy

Rothenberg et al (257)	RCT	CRC	627	130mg/m^2 over 2h q21 for 8 cycles (n=311)	85mg/m^2 over 2h q14 for 12 cycles (n=308)	Capecitabine as XELOX in 3-weekly treatment and 5FU/LV as FOLFOX4 for 2-weekly	NCI CTC	40 (12)	17 (5)	1 (<1)	50 (17)	14 (5)	5 (2)	No stated exlusion for pre-existing PN	XELOX versus FOLFOX rather than simply scheduling of oxaliplatin	No significant difference reported
Scheithauer et al (255)	RCT	CRC	89	130mg/m2 over 2h q21 for 8 cycles (n=45)	85mg/m2 q14 for 12 doses (n=42)	Capecitabine different schedules	WHO	36 (80)	23 (52)	7 (16)	35 (83)	19 (45)	5 (12)	No mention of clinical confounders	Different doses of capecitabine	No significant difference

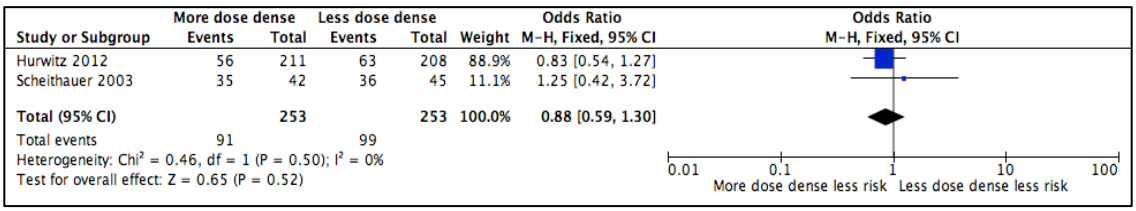


Figure 2.11. Forest plot demonstrating risk of development of any grade CIPN with more dose dense oxaliplatin (all patients receiving concurrent oxaliplatin and capecitabine)

It can be seen from figure 2.11 that there is very little difference to be seen in these studies between the neurotoxicity of two- versus three-weekly oxaliplatin when given with capecitabine.

Meta-analysis was not performed for the XELOX versus FOLFOX studies due to the differences described above. The only two studies which could be combined in the meta-analysis based on consistency of study design and doses were the studies by Cassidy et al (256) and Rothenberg et al (257); however their hugely different neurotoxicity rates and lack of description of acute versus chronic neurotoxicity would make combining results questionable.

Ixabepilone

Two studies were identified (table 2.11), one with a sample of 171 (260) patients and one with a sample size of 90 (261). Both were in the setting of advanced breast cancer and focussed on overall response rate (261) and 6 month progression free survival (260), respectively. One was designed as a comparative study, whilst one was a randomised, non-comparative study (261). Both allowed patients with pre-existing neuropathy to enter, albeit one excluded those with greater than grade 1 symptoms at trial entry (260). Both considered that prior taxane may be relevant to their results. The schedules of ixabepilone were similar but not exactly the same. The numbers of patients experiencing CIPN in the studies have been entered into a meta-analysis, but the slight differences in treatment plan need to be considered a limitation of pooled data results (figure 2.12).

Table 2.11. Included ixabepilone studies for systematic review of dose dense versus less dose dense schedules and effect on risk of CIPN

Paper	Study type	Primary cancer	Sample size	Less frequent regimen (no. of patients)	Dose-dense regimen (no. of patients)	Any concurrent chemo	Grading tool	Frequency of CIPN (by grade)						Are patient factors considered	Are other treatment related factors considered	Difference
								Less dose dense			**More dose dense**					
								Any	**2-4**	**3-4**	**Any**	**2-4**	**3-4**			
Rugo et al (261)	Randomised non-comparative trial	Breast	90	40mg/m^2 over 3h q21 for 4 cycles then 32mg/m^2 over 3h q21 until progression or unacceptable toxicity (n=45)	16mg/m^2 over 1h weekly until progression or unacceptable toxicity (n=45)	Bevacizumab	NCI CTC	36 (80)	-	11 (24)	34 (76)	-	8 (18)	No exclusion criteria for clinical confounders. Stratifies for prior taxane only	Different schedule of bevacizumab in the dose dense group otherwise standard	Not set up for comparison
Smith et al (260)	RCT	Breast	171	40mg/m^2 over 3h q21 until progression or unacceptable toxicity (n=89)	16mg/m^2 over 1h on days 1,8,15 q28 until progression or unacceptable toxicity (n=82)	Nil	NCI CTC	38 (43)	24 (27)	14 (16)	26 (32)	17 (21)	7 (9)	Pre-existing PN> grade 1 was excluded. No other clinical confounders mentioned. Similar proportion of patients with prior taxanes in each arm	All treatment standardised	No significant difference reported

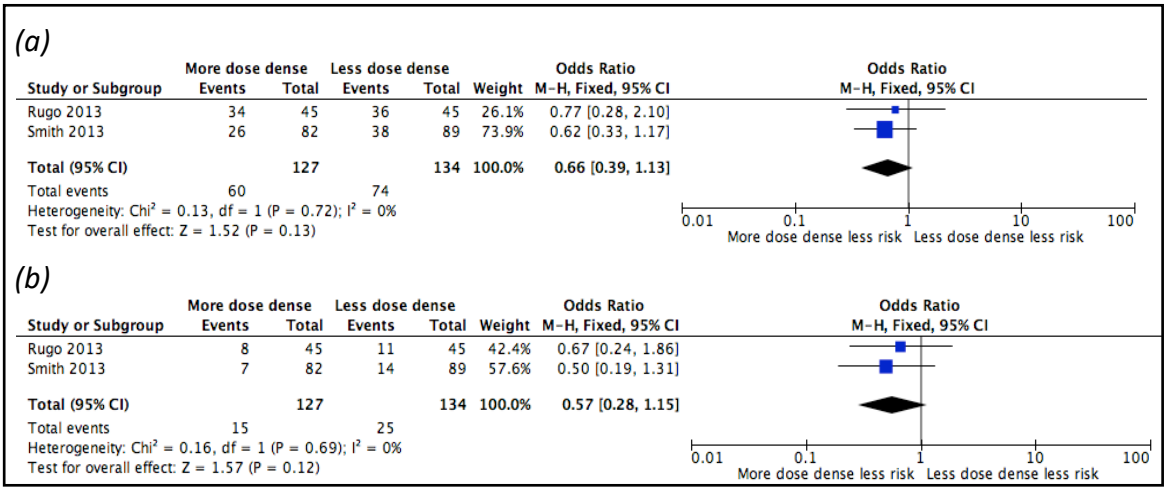


Figure 2.12. Forest plot demonstrating risk of development of (a) any CIPN and (b) NCI CTC grade 3-4 CIPN with more and less dose dense ixabepilone schedules, respectively

Looking at the forest plots, it can be seen that the combined study data suggests a trend to more dose dense scheduling being less neurotoxic. Only 261 patients were involved in the pooled population, however, which is clearly a limitation.

Vincristine

No studies examining dose-density of vincristine were identified. Dosing of vincristine is far more uniform at an almost universal dose of 1.4mg/m^2, generally capped at a total dose of 2mg due to the occurrence of CIPN. Studies of dose intensity were available investigating two-weekly versus three-weekly R-CHOP (Rituximab, Cyclophosphamide, Vincristine, Doxorubicin and Prednisolone combination therapy for Non-Hodgkin Lymphoma). These showed no significant difference in the neurotoxicity of the different regimens (262-264) but did not meet inclusion criteria for the search strategy.

2.4 DISCUSSION

The results for the systematic reviews of how diabetes and alcohol intake influence the risk of CIPN showed no conclusive outcome and were not amenable to meta-analysis. A general limitation of the included studies was that most were retrospective, and many had only a very small number of patients with the diagnosis/ exposure of interest.

Overall, there is no clear answer as to whether diabetes affects susceptibility to CIPN. Most studies were small and confounding factors were rife. Of the larger series, the cohort of 1587 colorectal cancer patients treated with oxaliplatin had some strengths in that all patients had a standardised dose and schedule of the neurotoxic agent, but unfortunately, the lack of differentiation of acute or chronic neuropathy is a limitation. This likely results from its retrospective nature making these more subtle but important clinical differences more challenging (216). The second largest study in this category gives an overall impression of the neurotoxicity of platinum- based chemotherapy for lung cancer in general. However, the results pertaining to risk associated with diabetes may be confounded by the differential neurotoxicity of the chemotherapy with some patients receiving two neurotoxic drugs rather than one.

There does not appear to be sufficient evidence to change treatment decisions with regard to neurotoxicity for diabetic patients who do not have pre-existing symptomatic neuropathy. A prospective study to determine the influence of diabetes on neuropathy risk using validated assessment tools is needed in view of the prevalence of diabetes in the population and the potential morbidity associated with neuropathy. Ideally, such a prospective study should include screening for diabetes at the start of chemotherapy as it has been reported that 18.5% of diabetes cases are undiagnosed, translating into an estimated prevalence of undiagnosed diabetes of 1.7% (265). This is particularly important given the use of steroids during chemotherapy which may result in hyperglycaemia. It would be important to collect data on other postulated risk factors and standardise treatment. Data on BMI and BSA would also be important to collect due to reports that higher BMI (106) or BSA (91, 96) may increase the risk of CIPN, and the clear potential crossover with diabetes risk. If BMI or BSA was found to be

associated with risk of CIPN this may have implications regarding dosing of taxane or oxaliplatin chemotherapy in obese patients.

Further study into the effects of alcohol would be more challenging. As demonstrated in the identified studies, definition of alcohol excess is not straightforward and would be unlikely to satisfactorily account for an individuals' historical alcohol consumption. From the systematic review, there is a suggestion that sustained alcohol excess resulting in liver disease may be associated with increased risk but it could postulated that this was due to other factors such as reduced metabolism of the drugs.

In terms of scheduling for taxanes, in doses in standard UK practice, the suggestion from these meta-analyses is that, for docetaxel there is no convincing effect of dose density on neuropathy risk however for paclitaxel the results seen largely suggest that more dose dense, weekly schedules are associated with a lower risk of CIPN. Heterogeneity of dosing in the studies identified however, effects the validity of conclusions. The choice of drug scheduling is at present very much more likely to be determined by efficacy concerns rather than toxicity.

With regard to oxaliplatin, simply changing schedule of oxaliplatin from two weekly to three weekly does not appear to change the incidence of neurotoxicity based on two studies (254, 255) and meta-analysis within this review. Two prospective non-randomised studies however, raised an interesting finding, that two weekly oxaliplatin regimens with intravenous 5-FU were more neurotoxic than the XELOX regimen (259, 266). As fluoropyrimidines are only rarely associated with neuropathy, the difference seen in the non-randomised studies between FOLFOX and XELOX is unexpected given the lack of differential neurotoxicity seen in the purely scheduling studies. It raises the question as to whether the choice of fluoropyrimidine in fact alters the neurotoxic potential of the regimen. One of the randomised controlled studies supports this finding with XELOX causing less grade 3-4 sensory neurotoxicty, but the study was limited by the unusually high dose of oxaliplatin (100mg/m^2) in their FOLFOX regimen (258). The larger randomised controlled trials do not support this finding with no significant difference seen. Numerically there are more cases of grade 3-4 neuropathy

seen in the Rothenberg study (5 cases in the FOLFOX group, 2% versus 1 case in the XELOX group, <1%) (257) but this was not statistically significant. The largest RCT did not show any such trend (256). The strength of the randomised controlled trials is clearly their superior methodology and their size. However, as they are designed to look at efficacy outcomes rather than toxicity, they are limited by their lack of consideration to pre-existing neuropathy or its risk factors and the lack of accurate description of the neurotoxicity outcome in question. To answer the question raised in this review regarding increased neurotoxicity of FOLFOX compared with XELOX, it would require a randomised study but with chronic neurotoxicity as a specified outcome with assessments of chronic neuropathy at each cycle and after completion of therapy using a validated assessment method. Such a study should also ideally incorporate patient related outcome measures.

Oxaliplatin-induced chronic neuropathy is a difficult to manage, treatment-limiting effect commonly seen in colorectal cancer management. If it were to be confirmed that FOLFOX results in less neurotoxicity, this may have a large impact on choice of regimen particularly in the adjuvant setting and reduce the burden of this adverse effect on survivorship without compromising efficacy of the regimen. The barrier to such a study would be that other factors such as the need for an indwelling venous line for 5FU, differential risk of mucositis and diarrhoea may effect interest and therefore recruitment to any such study.

2.5 CONCLUSION

There is insufficient evidence at present to clearly define an at-risk group of patients for the development of CIPN with taxanes, oxaliplatin or vincristine. As discussed through the literature review in Chapter 1, African American patients may be at higher risk of vincristine related neuropathy and patients with a high BMI may also be at greater risk of CIPN in general. The factors systematically reviewed in this chapter are not clearly related to increased risk of CIPN, but further study of the influence of diabetes and BMI would be of particular value. Treatment factors such as total cumulative dose, dose per cycle and duration of infusion are important but more prospective studies are

warranted to explore inter-individual risk based on patient-related factors and these have been outlined above. Other factors needing investigation include genetic variation either in pathways determining drug metabolism or in pathways that may influence susceptibility of nerves to damage or impede recovery mechanisms. This is dealt with in chapters 3 and 4.

CHAPTER 3

THE MOLECULAR GENETICS OF CHEMOTHERAPY-INDUCED PERIPHERAL NEUROPATHY: A SYSTEMATIC REVIEW

3.1 INTRODUCTION

As well as considering clinical risk factors for developing CIPN, inter-individual differences in drug effects may also be affected by genetic variation. It can be speculated that differences in various aspects of the process of metabolism of the drug may be affected by genetic variation in individuals and impact on the exposure of the individual to the drug, its efficacy and its toxicity. This could be in phase I metabolism (variations altering cytochrome P450 (CYP) enzyme activity), phase II metabolism (variations altering glucuronidation) or drug transport affecting elimination processes (alterations in efflux carriers for example, the ATP-binding cassette (ABC) transporters in the cell membranes of hepatocytes, or import carriers, such as organic anion transporter (OAT) in cell membranes of renal tubule cells and hepatocytes). It may also be hypothesised that genetic variations in the target tissues will determine susceptibility to efficacy or toxicity.
There have been concerns in the literature regarding methodological quality of pharmacogenetics studies (267) so whilst examining available study results it is also important to evaluate the strength of that evidence.

Increasingly there have been pharmacogenetics studies investigating genetic variants which may predispose to CIPN. This systematic review will aim to evaluate the current evidence on the effect of genetic variants on the development of CIPN, which SNPs have been studied, and the quality and strength of this evidence.

3.2 METHODS

Search strategy

Medline, Scopus, CINAHL, and the HuGENet database were originally searched on 23/02/2014 applying the strategy outlined in table 3.1 but repeated on 20/01/2016.

Table 3.1. Details of search strategy

Number	Search term
1	chemotherapy.mp
2	paclitaxel.mp
3	docetaxel.mp
4	taxane.mp
5	oxaliplatin.mp
6	cisplatin.mp
7	platinum.mp
8	vincristine.mp
9	vinc*.mp
10	geno*.mp
11	genetic*.mp
12	pharmacogen*.mp
13	haplotyp*.mp
14	variant.mp
15	allel*.mp
16	SNP.mp
17	polymorphism.mp
18	neurotoxicity.mp
19	*peripheral neuropathy*.mp
20	neuropath*.mp
21	*sensory impairment*.mp
22	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9
23	10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17
24	18 OR 19 OR 20 OR 21
25	22 AND 23 AND 24

mp= title, original title, abstract, name of substance word, subject heading word
*= any ending to the word

Study selection

Studies reported in English in populations undergoing cancer treatment with cytotoxic chemotherapy known to be associated with CIPN, which investigated an association between one or more genetic factors and neuropathy outcomes were included. The scope of the review was limited to cytotoxic chemotherapy and studies of novel,

biological agents, such as bortezomib or thalidomide were excluded. Case studies were also excluded.

The search results were compiled, duplicates removed and screened (JC). Papers that were clearly not relevant were excluded by title or abstract and for the remaining, potentially relevant studies, full papers were examined (JC) to identify the final set of manuscripts meeting the inclusion criteria. Bibliographies of included studies were checked for overlooked papers. Care was taken to identify the authors, geographical location and time period of the study to minimise the risk of including the same dataset more than once. If the same or overlapping datasets were identified in multiple publications, the larger dataset was included for meta-analysis purposes.

Data extraction

Relevant methodological and clinical data were collected through use of a data extraction form developed with reference to both the HuGeNet Reviews Handbook (268) and a specialist review of methodological issues in pharmacogenetic studies(267). The forms were piloted on five studies and once amendments were made, they were completed for each study by two independent reviewers (JC plus either LC or FA). Any discrepancies were referred to a third reviewer (RL or DC).

Statistical analysis

The studies were grouped by class of chemotherapy drug investigated and the genetic variants examined. Where multiple studies investigated the same SNP for the same drug, providing they reported the numbers of patients with or without neuropathy per genotype, they were combined in a meta-analysis. Forest plots were prepared using RevMan V5.0 (269) using the Mantel-Haenszel method and assuming a random effects model to allow for heterogeneity. Extent of heterogeneity between studies was estimated using the I^2 statistic. Plots were stratified for ethnicity as recommended by HuGENet (268) with effect sizes both per ethnic stratum and overall estimated. Where ethnicity was not stated in the study, the predominant ethnicity represented was

assumed depending on the country of origin of the study. For the purpose of calculating the effect estimate, a dominant mode of inheritance was assumed, i.e. the effect estimate represented that for heterozygotes and mutant homozygotes combined versus wild-type homozygotes as this was in line with the majority of published papers.

3.3 RESULTS

After applying the search strategy, 1779 titles were identified after removal of duplicates with a further 15 articles identified for review from hand searching reference lists from review articles. From these, 134 warranted full text review and 93 met criteria for inclusion (Figure 3.1). Three relevant abstracts were identified with no full text article yet published. These will be mentioned but were not included in our full analysis (86, 270, 271). Two papers were identified in Japanese but unfortunately translation was not possible and they were excluded as pre-stated.

93 studies were therefore included in the systematic review. Five of these were genome wide association studies (72, 82, 85, 272, 273), a sixth presented selected genotyped and imputed results from a genome wide association study but the full GWAS results were not published (274). 16 studies investigated SNP(s) in a single candidate gene (71, 73, 275-289) The remainder of the studies studied multiple candidate SNPs in one or more genes. Six studies were conducted in a paediatric population (72, 73, 289-292) the remainder in adults.

Two studies compared chemotherapy to chemotherapy combined with a targeted agent with neurotoxic potential (thalidomide (276) and bortezomib (293) respectively). For these papers only the chemotherapy-alone arm was included in this review.

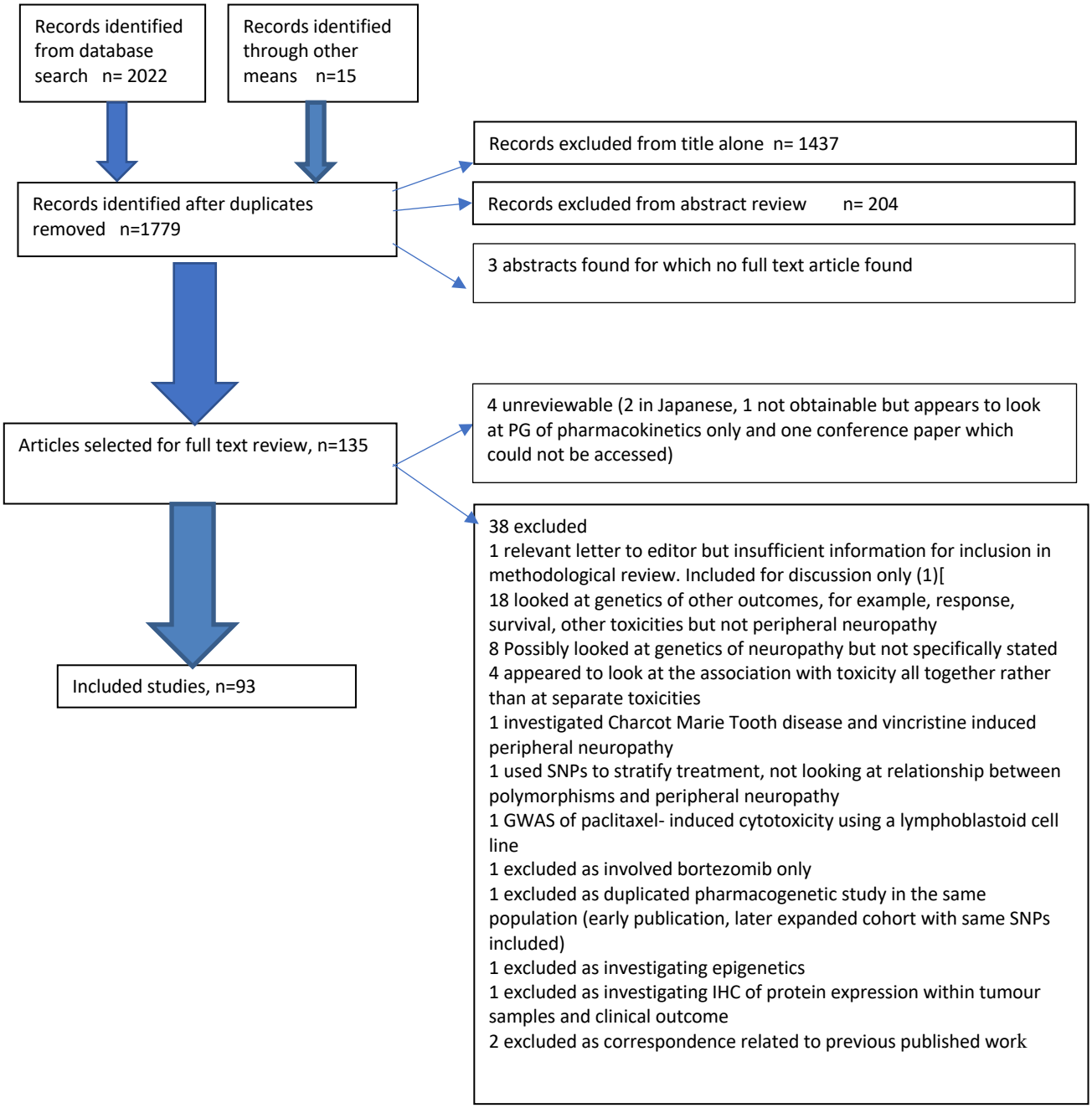


Figure 3.1. Flow of identified references

3.3.1 Assessment of methodological quality of included studies

The results from assessing the included papers against the methodological checklist are summarised below.

Sample size

Nine studies included both a discovery set and a replication set (72, 82, 100, 272, 273, 294-296). Another four (297-300) studies included two treatment arms which were analysed separately, each involving either a different potentially neurotoxic agent, or the same potentially neurotoxic drug but in a different schedule. One of these studies also separated their cohorts into discovery and replication cohorts (299). A further study analysed their cohort in separate groups according to ethnicity (281) All of these patient cohorts are treated separately for the purposes of investigating sample size. With these considerations taken into account, the median sample size was 118.0 (IQR 73-209). Only six studies mentioned an a priori sample size calculation (73, 277, 280, 301-303). One study made a post-hoc estimation of power (304) and a further study stated upfront the minimal odds ratio detectable given their sample size (88).

Study design

Of the 93 included studies, 43 were prospective cohort studies (82, 88, 90, 98, 272, 274, 276, 277, 280, 282, 283, 286, 288, 291, 293, 297, 298, 300, 302-326) and 22 were retrospective analyses from cohorts with clearly described, prospectively recorded clinical data, many part of a separate prospective clinical trial (72, 85, 89, 100, 273, 275, 279, 287, 290, 295, 299, 327-336); 21 were retrospective cohort studies (71, 73, 94, 95, 215, 217, 278, 281, 284, 285, 289, 294, 296, 337-345) and one study included a mix of prospectively and retrospectively recruited patients (301). Five were case-control studies (41, 103, 292, 346, 347), one of which used a control group of healthy blood donors who had not been exposed to the potentially neurotoxic agent (346).

Selection of investigated genes

In general, all studies provide some explanation for the selection of genes chosen for investigation. Explanations for the selected SNPs were occasionally absent. Some papers provided a very broad statement, usually a necessity when many associations are being sought.

Reliability of genotypes

Method of genotyping was reported in all studies, although in some the description was very brief allowing only limited assessment of quality. In 56 (60%) of the studies there was no mention of specific quality control procedures being undertaken. Only 29 studies state that genotyping personnel were blinded to clinical outcome data. 39 (42%) of the non-genome wide studies (90, 94, 95, 276, 278, 280-282, 284, 288, 290, 292, 297, 299-303, 305, 311, 315, 316, 318, 319, 321-324, 329, 330, 332, 333, 336, 337, 342, 344-346, 348) compared their genotyping results to previously published data, which may be used as a basic method of looking for problems with genotyping.

Six of the studies carried out genotyping on formalin fixed paraffin embedded (FFPE) tumour samples (277, 278, 332, 336, 343) or peritumoural tissue (294) rather than peripheral blood samples. There is some controversy over whether tumour sample genotyping is a reliable method for this type of study and whether results obtained from such samples and those obtained from peripheral blood can be considered comparable. Some authors have demonstrated almost complete concordance in genotyping certain genes in blood and FFPE tumour samples (349, 350) whereas others have shown more discrepancy (351).

Missing genotype data

For 29 of the 87 non-GWA studies it is clear that no genotyping data was missing (71, 88, 89, 94, 215, 276-280, 284, 288, 289, 291, 305, 308, 309, 311, 313, 314, 325, 327, 329, 331, 335, 337, 338, 348). For the six studies utilising a genome wide approach (72, 82, 85, 272-274) and four studies which genotype a large array of SNPs (293, 295, 296, 328) parameters for excluding SNPs or subjects were clear. For 39 studies some missing genotype data was evident (41, 73, 90, 95, 98, 100, 103, 217, 276, 282, 283, 292, 294, 297-300, 302, 306, 307, 310, 312, 316-320, 322-324, 332, 333, 336, 341-344, 346, 347),

but only in six of these was there an explanation for missingness (100, 282, 322-324, 343). For 16 studies, it cannot be determined from the information provided whether or not there is missing genotype data (281, 285-287, 290, 301, 303, 304, 318, 321, 326, 330, 339, 340, 345). In no study was there evidence of checks that data was missing at random.

Population stratification

Only seven studies (7.5%) mentioned accounting for population stratification (72, 82, 274, 291, 295, 296, 328). Five used principle component analysis (72, 82, 274, 295, 296), the sixth genotyped ancestry informative markers and correlated these with self-reported race (291). The seventh study also included SNPs to estimate individual ancestry and stated that population admixture proportions were determined using Bayesian clustering algorithms (328).

40 studies involved a single ethnic group; 25 Caucasian populations (85, 89, 90, 103, 217, 273, 274, 278, 280, 289, 290, 294, 301, 304, 305, 308, 318, 333-338, 343, 344) and 15 East Asian populations (94, 272, 286-288, 302, 311, 314, 315, 319, 324, 327, 331, 341, 348). 22 studies involved mixed populations (41, 71-73, 82, 95, 98, 100, 279, 281, 291, 292, 296, 300, 321-323, 328, 330, 332, 342, 347) and in 31 studies ethnicity was not mentioned. In the 22 mixed ethnicity studies, one study analysed their cohort by separate ethnic groups (281), five accounted for this by population stratification (72, 82, 291, 296, 328) and four studies adjusted for ethnicity in their analysis (292, 300, 330, 347). The remaining 12 did not appear to account for the mixture.

Hardy Weinberg Equilibrium

61 of the 93 included studies stated that they checked that genotypes were in HWE (82, 85, 88, 89, 94, 95, 98, 100, 103, 272-274, 276-279, 281, 284, 286, 287, 290, 293-306, 312-315, 318, 320-325, 328-330, 333, 334, 336, 337, 339, 341-344, 348).

Mode of inheritance

For three studies, this point is not applicable (229, 280, 288) (one looking at the length of the common allele containing a CAG motif (280), for one no homozygote wild-type patients existed (288) and for one no homozygote variants existed (331). In the remaining 89 studies, 25 studies (71, 85, 88, 89, 217, 271, 289, 295-297, 301, 303, 304, 318, 320-323, 328, 330, 336, 342-344, 347) made a clear specific statement about how they were going to analyse their genotype data with regard to mode of inheritance. However, six of these stated that they were analysing using more than one type of assumption (88, 297, 303, 304, 343, 347). In 28 studies (94, 95, 100, 274, 279, 284-286, 291, 294, 307, 309, 311, 313, 315, 316, 318, 319, 323-325, 327, 329, 335, 338, 341, 345, 348), although not explicitly stated, it was apparent from the results which mode(s) had been assumed. In the remaining studies, assumed mode(s) could not reliably be determined.

Multiple testing

Only three studies clearly did not require adjustment for multiple testing (one SNP, one outcome, one mode of inheritance clearly stated) (280, 281, 289). Of the remainder, 21 made an adjustment for multiple testing (41, 72, 89, 217, 286, 287, 291-293, 295, 304, 308, 315, 321, 328, 330, 337, 342-344, 347). All GWAS set appropriate levels of significance to reflect the multiple tests involved.

The lack of adjustment is particularly important to note where studies are reporting positive results (71, 90, 94, 95, 98, 100, 276, 285, 294, 298, 300, 301, 305-307, 319, 325-327, 338, 341, 348) or a trend towards a positive result (275, 316, 340). All of the genome wide association studies set appropriate levels of significance to reflect the multiple tests involved.

3.3.2 Chemotherapy and clinical considerations and their impact on phenotype definition

Chemotherapy factors

The neurotoxic drugs studied are summarised in table 3.2.

Table 3.2. Summary of drugs investigated (total adds up to >93 as some studies included more than one neurotoxic drug)

Neurotoxic Drug	Number of studies
Oxaliplatin	35 (88-90, 94, 95, 272, 273, 277-280, 294, 297, 298, 300, 302-304, 306, 307, 309, 311-314, 316, 319, 320, 325, 327, 331, 332, 339, 348)
Oxaliplatin OR cisplatin	1 (215)
Cisplatin	6 (282, 286, 298, 308, 338, 347)
Cisplatin OR carboplatin	4 (98, 217, 287, 343)
High dose carboplatin	1 (78)
Paclitaxel (some with carboplatin)	29 (82, 85, 100, 274, 275, 281, 283, 285, 288, 296, 299, 301, 305, 315, 318, 321-323, 326, 328, 330, 334-336, 340, 342, 344-346)
Docetaxel (some with carboplatin)	4 (103, 276, 299, 329)
Paclitaxel OR docetaxel (some with carboplatin)	3 (295, 337, 341)
Docetaxel AND cisplatin	1 (317)
Vincristine	11 (41, 71-73, 284, 289-293, 324)
Ixabepilone	1 (310)

A major methodological flaw noted was that in some of the cohorts some patients were receiving multiple concurrent neurotoxic drugs. In two of the cisplatin studies, some of the patients received vinblastine concurrently (338, 347), and in one study, some of the patients concurrently received either vindesine or docetaxel (286). In four studies, either carboplatin or cisplatin were used as the index drug (98, 217, 287, 343) notwithstanding it is well established that carboplatin is significantly less neurotoxic than cisplatin. In two of these studies, to further compound the issue of differentially neurotoxic treatments, some patients concurrently received paclitaxel (217, 343). Paclitaxel and a platinum are often concurrently given, but in two of the paclitaxel

studies, only some of the patients received concurrent cisplatin whilst others received the far less neurotoxic carboplatin (285, 301) . Another study looked at the combination of two highly neurotoxic drugs, docetaxel and cisplatin in all patients (317). Where treatment was uniformly with two neurotoxic agents, conclusions can only be drawn about the combination treatment rather than the individual drugs involved.
In addition, some studies included different drug regimens (82, 88, 89, 95, 100, 103, 272, 280, 281, 285, 294, 296, 301, 303, 305, 310, 321-324, 326, 328, 330, 333, 335, 338, 340, 342, 343, 346). Some studies adjust for this (72, 95, 100, 103, 294, 295, 298, 301, 333, 338, 347) but others did not leading to confounding as different regimens of the same drug may be differentially neurotoxic (226, 237, 242, 243, 247).
For instance, some investigators have shown that FOLFOX4 is a more neurotoxic regimen than XELOX (259) and a number of studies have demonstrated differential neurotoxicity of weekly versus three-weekly taxanes (226, 237, 242, 243, 247), albeit some are contradictory.

A further limitation is that a significant proportion of studies did not make it clear that definitions were set regarding a minimum dose of neurotoxic drug received to be classified as a control. For example in the majority of studies there was no assurance that consideration was given to patients who may have stopped chemotherapy early due to other toxicities or disease progression.
24 studies stated clear appropriate minimum dose criteria (95, 215, 272, 277-280, 287, 288, 293, 295, 302, 305, 316, 319-323, 325, 331, 335, 342, 343). Other studies adjusted for total dose received (88, 289, 294, 338, 347, 348) or used cumulative dose (82, 85, 274, 281, 285, 296, 301, 336, 340, 345) or a time point in their outcome (71, 100, 105, 275, 276, 318, 334); however for 45 studies, this was left as a potential source of inaccurate phenotyping. One case-control study chose their control group from a population of healthy volunteers with no exposure to the neurotoxic agent (346).

Other clinical considerations

Baseline characteristics

24 studies excluded all patients with a history of symptomatic peripheral neuropathy (85, 88-90, 94, 95, 103, 217, 272, 277, 278, 280, 294, 295, 300, 301, 304, 321-323, 326, 327, 342, 345). A further nine excluded those with ≥grade 2 peripheral neuropathy at baseline (71, 283, 293, 298, 299, 310, 336), a peripheral neuropathy score of >3 (275) or disabling peripheral neuropathy (348).

The remaining studies made no mention of excluding patients with pre-existing neuropathy. Whether the risk of developing CIPN was affected by diabetes or excessive alcohol intake is controversial but only a few studies acknowledged these factors by excluding affected patients or considering either diabetes (94, 103, 281, 286, 290, 296, 301, 308, 321, 323, 329, 345) or alcohol excess (103, 277, 278, 280, 301, 327, 345), as covariates.

Assessment of neuropathy

There was variation found in terms of assessment of neuropathy and neurotoxicity endpoints used. The majority of studies (63/93) used NCI CTC grading to document presence and severity of neuropathy. Six studies of oxaliplatin induced peripheral neuropathy used the oxaliplatin specific scale (95, 298, 302, 304, 316, 320) and three studies each used the WHO toxicity grading scale (273, 282, 317) and Total Neuropathy Score (TNSc) (88, 277, 278), respectively. One study used both NCI CTC and TNSc (89) and one used both the NCI CTC and oxaliplatin grading scale (298). Two paediatric studies used the Children's Cancer Group toxicity grading system (41, 292) and one used a global toxicity score (290). Two studies correlated genotype information with results of neurophysiological testing (215, 280). Six studies used other lesser known scales including a PNP score (275) a 'specific neurotoxicity score' (306), the scale for CIPN (SCIN) (338), a neurotoxicity scale resulting in an 'N score' (305), the Michigan neuropathy screening instrument (347) and one defined by the authors in their text which appeared consistent with NCI CTC (300). Three studies performed by the same

group used the EORTC CIPN20 scale to define case and control groups. Questionnaires were completed by patients at consecutive cycles and their results plotted. They used rate of change of scores to define cases with a significantly increased rate of change and controls, with a significantly slower rate of change and excluded those that approximated to the median rate of change slope (321-323). The measurement tool used was not stated in four of the studies (310, 314, 315, 318). The various methods of documenting presence and severity of neuropathy are outlined in table 3.3.

Table 3.3: Methods of assessment of CIPN

	Assessment tool
NCI CTC	63
WHO	3 (273, 282, 317)
Oxaliplatin specific scale	6 (95, 298, 302, 304, 316, 320)
TNSc	3 (88, 277, 278)
CCG	2 (41, 292)
Neurophysiological methods	2 (215, 280)
Other score	10 (275, 290, 300, 305, 306, 321-323, 338, 347)
Not clear	4 (310, 314, 315, 318)
More than one grading scale stated	2 (89, 298)

NCI CTC= National Cancer Institute Cancer Common Terminology Criteria, WHO= World health Organisation, TNSc= Total Neuropathy Scale clinical, CCG= Childrens Cancer Group

Different groups looked at different CIPN outcomes including occurrence of any grade, $\geq$ grade 2 or $\geq$grade 3 CIPN or either time to neuropathy or cumulative dose at occurrence of grade 2 neuropathy. In 57 studies, outcomes were pre-specified, whilst in others (28/93), this became apparent in the results, and in the remainder the neuropathy outcome was not clearly defined (8/93).

Acute versus chronic oxaliplatin neurotoxicity

An issue specific to oxaliplatin studies is that consideration is required of the two distinct forms of neuropathy that it is associated with. An acute neurotoxicity which occurs in the majority of patients treated often occurs immediately following administration, is transient and associated with dysaethesia on exposure to cold. A chronic, cumulative form of neuropathy affects a smaller proportion of patients and develops after repeated dosing. Acute neurotoxicity may be due to a channelopathy,

whereas it is thought that the chronic form of neuropathy is likely to be due to accumulation of platinum in the dorsal root ganglion. As it is likely that different mechanisms are responsible for each form of neurotoxicity, studies investigating a pharmacogenetic association of increased risk should clearly define which form of the toxicity they are investigating. Fifteen studies specifically looked at chronic neurotoxicity (88-90, 94, 95, 215, 272, 277, 278, 294, 297, 316, 320, 325, 327) and one study specifically looked at acute neurotoxicity (280). The remaining 19 studies did not explicitly make a differentiation. The oxaliplatin specific scale is scored in a way that at least in part differentiates acute and chronic neuropathy by taking into account the duration of symptoms, however only three (298, 302, 304) of the 19 studies used this.

3.2.3 Genetic associations investigated and meta- analysis

The array of SNPs investigated was extensive but what follows is a presentation of SNPs which have been investigated in numerous studies for certain drug classes. All included studies are summarised in tables 3.4-3.8. Where meta-analyses have been performed this is stated in the text. Table 3.9 details which meta-analyses were performed and reasons why others were not.

Table 3.4. Included oxaliplatin-based studies for systematic review of pharmacogenetics of CIPN

First author (Year)	Index drug(s)	SNPs investigated (those underlined highlight statistically significant ssociations)	Country	Ethnicity	Ethnicity uniform, mixed-adjusted for or mixed	Test for population substructure	Primary tumour	Assessment tool for CIPN	CIPN endpoints investigated	Sample size (number of 'cases' according to the authors definition)	Schedule/ dose uniform, adjusted for or mixed	Minimum dose for controls	Potential clinical confounders accounted for	HWE checked	Genotype QC measures described	Mode of inheritance used in analysis stated	Multiple testing adjustment
Antonacopolou (2010)	Oxaliplatin	*ITGB3 L33P*	Greece	NS	NS	No	CRC	TNSc	Development of neuropathy	55 (34)	Uniform	Yes	Excludes pts with pre-existing PN, DM, alcohol abuse	Yes	Yes	Evident in results (recessive model)	Single SNP
Argyriou (2009)	Oxaliplatin	*SCN2A R19K*	Greece	European	Uniform	No	CRC	TNSc	Development of any grade and grade 1 vs grade 2	62 (36)	Uniform	Yes	Excludes pts with pre-existing PN, DM, alcohol abuse	Yes	NS	Unclear	Single SNP
Argyriou (2013)	Oxaliplatin	*SCN4A (rs2302237)*, *SCN9A (rs67406030), SCN10A (rs12653942, rs6800541)*	Greece, Spain, Italy	NS	NS	No	CRC	TNSc	Development of neuropathy and severity	200 (145)	Adjusted	Dose used in outcome	Excludes any pre-existing PN	Yes	NS	Yes (3 modes used in analysis)	No
Basso (2011)	Oxaliplatin	*SK3 CAG* motif polymorphism	Italy	Caucasian	Uniform	No	CRC, pancreas and biliary	clinical examination, NCS and needle EMG	Neurophysiological change	40 (28)	Mixed	NA, Acute neurotoxicity	All pre-existing PN and alcohol abuse excluded	Yes	NS	Not applicable	Single outcome
Boige (2010)	Oxaliplatin	20 SNPs in *ERCC1, XPD, GSTM1, GSTT1, GSTP1, UGT1A1, TS, MTHFR*	NS	NS	NS	No	CRC	NCI CTC	Development of grade 2-4 neuropathy	Sequential chemo arm: 132 (66) Combination chemo arm: 175 (111)	Uniform	No	No	NS	NS	Yes (more than one mode used)	No
Cecchin (2013)	Oxaliplatin	57 SNPs in 29 genes incl *ABCB1, ABCC1, ABCC2, ABCG2, GSTP1, GSTT1, GSTM1, ERCC1, XPD, XRCC1, SCN2A* and *AGXT*	Italy	Caucasian	Uniform	No	Colorectal	Oxaliplatin specific scale	Development of grade 2-4 neuropathy	144 (56)	Uniform	No	Excluded any pre-existing PN and any concurrent neurotoxic drugs	NS	NS	Analysed using three models and most significant was reported	Yes
Chai (2012)	Oxaliplatin	*GSTP1 Ile105Val, ERCC1 C118T, XRCC1 Arg399Gln, ABCB1 (C3435T, G2677T/A), MTHFR C677T, UGT1A1 (*6,*27, *28), DPYD (*2,*5,*9), TYMS 6bpins/del*	China	Han Chinese	Uniform	No	CRC	NS	NS	73 (NS)	Uniform	No	No	Yes	Yes	Unclear	No
Chen (2009)	Oxaliplatin	*GSTP1 Ile105Val, ERCC C118T, XPD Lys751Gln*	Taiwan	Chinese	Uniform	No	CRC	NCI CTC	Development of grade 3-4	166 (33)	Uniform	No	Excluded pre-existing PN, DM or alcohol abuse	Yes	NS	Evident in results (dominant)	No

Chua (2009)	Oxaliplatin	*ERCC1 C118T, MTHFR C677T, XRCC1 Arg399Gln*	Australia	Mixed	Mixed	No	CRC	NCI CTC	Development of grade 3-4	118 (20)	Uniform	No	No	Yes	NS	Unclear	No
Cortejoso (2013)	Oxaliplatin	*ABCB1 (C3435T, G2677T/A, C1236T), ERCC1 C118T, XPD Lys751Gln, XRCC1 Arg399Gln, GSTP1 Ile105Val, GSTT1, UGT1A1 (G3156A, *28)*	Spain	NS	NS	No	CRC	NCI CTC	Development of grade 3-4	106 (13)	NS	No	No	NS	Yes	Unclear	No
Custodio (2014)	Oxaliplatin	34 SNPs in 15 genes incl *rs2230641* in *CCNH* and *rs3114018* in *ABCG2*	Spain	Caucasian	Uniform	No	CRC	NCI CTC	Development of grade 2 lasting for >7 days or grade 3	Exploratory 206 (48); validation 181 (72)	Adjusted	Dose used in outcome	Excluded those with pre-existing PN	Yes	NS	Evident in results (dominant and possibly some additive)	No
Fernandez-Rozadilla (2013)	Oxaliplatin	GWAS	Spain	Caucasian	Uniform	No	CRC	WHO	Development of grade 2-4 or grade 1 if cycles ≤4 or in cycles>4 and dose reduction or delayed based on time over expected length of course	133 phase 1 (47); 324 phase 2 (225)	NS	No	No	Yes	Yes	Unclear	Yes
Gamelin (2007)	Oxaliplatin	*GSTP1 (Ile105Val and Ala114Val), AGXT (154C>T, 155C del, 156Cins, Duplication 74bp intron 1, 576T>A, 588G>A, 630G>A, 640G>A, 819C>T, 820G>A, 853T>C, 860G>A, A1119T, A1142G), ABCC2 (24C>T, 3972C>T), GRHPR (103del, 295C>T, AAGTdel)*	France	French Caucasian	Uniform	No	CRC	NCI CTC	Development of grade 2-3	135 (28)	Uniform	No	Excluded pre-existing PN	Yes	NS	Unclear	No
Goekkhurt (2009)	Oxaliplatin and cisplatin	*GSTP1 Ile105Val, GSTM1, GSTT1, ERCC1 (C118T, C8092A), XPD (Lys751Gln, Asp312Asn), XRCC1 Arg399Gln, XPA A23G, TS (1494del6, VNTR 28bp repeat, VNTR +G/C SNP), MTHFR (C677T, A1298C), MTR A2756G, OPRT Gly213Ala*	Germany and Switzerland	NS	NS	No	Upper GI	NCI CTC	Development of grade 3-4	Oxaliplatin arm: 71 Cisplatin arm: 63 (12-15)	Adjusted and analysed separately	No	Excluded those with PN> grade 1	NS	NS	Unclear	No

Hong (2010)	Oxaliplatin	*ERCC1 (C8092A, C118T), XPD (Lys751Gln, Asp321Asn, C156A), XRCC1 (Arg399Gln, Arg194Trp, Arg280His), GSTP1 Ile105Val, AGXT (I340M), CYP2A6 (-48G/T), MTHFR A1298C, TS (TSER, 3'-utr and 5'G/C)*	Korea	NS	NS	No	CRC	NCI CTC	Development of grade2-4	52 (8)	Uniform	No	No	Yes	NS	Evident in results (dominant)	No
Kanai (2012)	Oxaliplatin	*GSTP1 Ile105Val, AGXT (Pro11Leu, Ile340Met)*	Japan	Japanese	Uniform	No	CRC	Oxaliplatin specific scale	Development of grade 2-3	82 (44)	Uniform	Unclear	No	Yes	NS	Unclear	No
Keam (2008)	Oxaliplatin	*GSTP1 Ile105Val, ERCC1 (C118T, C8092A), XPD (Lys751Gln, C156A, Asp312Asn), XRCC1 Arg399Gln*	Korea	NS	NS	No	Upper GI	NCI CTC	NS	73 (13 any grade; 1 grade 3-4)	Uniform	No	No	NS	NS	Evident in results (dominant)	No
Kumamoto (2013)	Oxaliplatin	*GSTP1 Ile105Val, GSTT1, GSTM1, ERCC1 C118T, ERCC2 Lys751Gln, MTHFR Ala677Val, TS 5'UTR VNTR, TS 3'UTR 6bp ins/del*	Japan	Japanese	Uniform	No	CRC	NCI CTC	Development of grade 2-4	63 (43-44)	Uniform	Yes	No	Yes	NS	Evident in results (dominant)	No
Kweekel (2008)	Oxaliplatin	*GSTP1 Ile105Val*	Netherlands	Mixed: mainly Caucasian	Mixed	No	CRC	NCI CTC	Development of any neuropathy and grade 3-4	91 (60 any grade, 5 grade 3-4)	Uniform	Yes	No	Yes	NS	Evident in results (appears looked at dominant, recessive and no assumption)	Single SNP
Lai (2009)	Oxaliplatin	*XPD Lys751Gln, TSER 28bp* polymorphism	Taiwan	Chinese	Uniform	No	CRC	NCI CTC	Development of grade 3-4	188 (30)	Uniform	Yes	No	Yes	NS	Not applicable	No
Lecomte (2006)	Oxaliplatin	*GSTP1 (Ile105Val, Ala114Val), GSTM1, GSTT1*	France	Mixed (White, African, Asian)	Mixed	No	CRC, upper GI and pancreas	Oxaliplatin specific scale	Development of grade 3	64 (15)	Adjusted	Yes	Excluded pre-existing PN	Yes	NS	Evident in results (one dominant, one no assumption, two recessive)	No
Lee (2013)	Oxaliplatin	20 SNPs in *GSTP1, GSTM1, GSTT1, ERCC1, XPD, XRCC1 (Arg399Gln),ABCC2,AGXT, TS, MTHFR*	Korea	Korean	Uniform	No	CRC	NCI CTC	Development of grade 2-4	292 (51)	Uniform	No. No. of cycles used as covariate	Exclude patients with a history of disabling PN	NS	Yes	Evident in results (dominant)	No
Li (2010)	Oxaliplatin	*GSTP1 Ile105Val*	China	NS	NS	No	Gastric	Oxaliplatin specific scale	Development of grade 3-4	92 (12)	Uniform	Yes	No	Yes	Yes	Yes (dominant)	Single SNP
Liu (2013)	Oxaliplatin	*GSTP1 Ile105Val, ERCC1 C118T, XPD Lys751Gln, XRCC1 Arg399Gln*	China	NS	NS	No	Upper GI	NCI CTC	Development of grade 3-4	126 (NS)	Uniform	Yes	No	NS	NS	Evident in results (dominant)	No

McLeod (2010)	Oxaliplatin	*ABCB1 (C1236T,C3435T, G2677T), ABCC1 (rs2074087, rs2230671), ABCC2 (rs717620, rs8187710, rs7080681, rs2273697, rs374066), ABCG2 C421A, CYP3A4 (*1B and *3), CYP3A5 (*3C and *6), DPYD (*2A, *5, *6, *9A), ERCC1 C118T, ERCC2 -1989A>G, 2133C>t, 2251 A>G, GSTM1, GSTP1 (Ile105Val and Ala114Val), MTHFR (C677T, A1298C, G1793A), TYMS (1494del, TSER), UGT1A1 (*93,*28), XRCC1 Arg399Gln.*	USA and Canada	Mixed (White, Black NOS, Asian, Hispanic, Other)	NS	No	CRC	'Parathesias that interfered with daily activities or caused disability were classified as grade 3 or 4, respectively'	Development of grade 3-4, probability of discontinuing treatment due to neurotoxicity, time to development of neurotoxicity	299 FOLFOX4 arm; 107 IROX arm (44 cases in total)	Uniform; arms analysed separately	No	Excluded all pre-existing PN	Yes	NS	Unclear	No formal adjustment, consideration given in interpretation
Nishina (2013)	Oxaliplatin	*GSTP1 Ile105Val, ERCC1 (C118T, C8092A), XPD (Asp312Asn, Lys 751Gln)*	Japan	Japanese	Uniform	No	CRC	NCI CTC	Development of any grade and 3-4	68 (65 any grade, 11 grade 3-4)	Uniform	No	No	Yes	NS	Evident in results (dominant)	No
Oguri (2013)	Oxaliplatin	*GSTP1 (Ile105Val), ERCC1 (C118T, C8092A), 9 SNPs in TAC1, FOXC1, ITGA1, ACYP2, DLEU7, BTG4, CAMK2N1, FARS2*	Japan	Japanese	Uniform	No	CRC	NCI CTC	Development of grade 2 lasting >7 days or grade 3-4 and time to development of grade 1	70 (22 grade 2 > 7 days or grade 3-4))	Uniform	No	Excluded all pre-existing PN	Yes	NS	Evident in results (dominant)	No
Pare (2008)	Oxaliplatin	*ERCC1 (C118T, G19716C, C8092A), XPD Lys751Gln, GSTP! Ile105Val, XPD (Arg194Trp, Arg280His, Arg399Gln)*	Spain	NS	NS	No	CRC	Oxaliplatin specific scale	Development of grade 2-3	126 (71)	Uniform	No	No	NS	Yes	Evident in results (dominant)	No
Ruzzo (2007)	Oxaliplatin	*GSTP1 Ile105Val, GSTM1, GSTT1, ERCC1 C118T, XPD (Arg399Gln, Asp312Asn), XRCC3 Thr241Met, MTHFR (C677T, A1298C), TS (VNTR and SNP and 6bp ins/del)*	Italy	NS	NS	No	CRC	Specific neurotoxicity scale	Development of grade 3	166 (17)	Uniform	No	No	Yes	NS	Unclear	No
Ruzzo (2014)	Oxaliplatin	*GSTP1 (Ile105Val), GSTM1, GSTT1, ERCC1 C118T, XPD (Lys751Gln, Asp312Asn), XRCC3 (Thr241Met), ABCC1*	Italy	NS	NS	No	CRC	NCI CTC	Development of grade 2-4 neuropathy	517 (132)	Mixed	No	No	Yes	No	Yes: dominant, recessive and additive	No

		(rs2074087), ABCC2 (rs3740066, rs1885301, rs4148386), MTHFR (C677T, A1298C), TS (VNTR and SNP and 6bp ins/del)															
Seo (2009)	Oxaliplatin	*GSTP1 Ile105Val, GSTM1, GSTT1, ERCC1 (C118T, C8092A), TS-UTR, multiple UGT1A1 SNPs.*	Korea	NS	NS	No	Upper GI	NCI CTC	Development of grade 3-4	75 (12)	Uniform	No	No	Yes	NS	Evident in results (dominant)	No
Terrazzino (2015)	Oxaliplatin	*Rs10486003, rs2338, rs843748, rs797519, rs4936453, rs12023000, rs17140129, rs6924717*	Italy	Caucasian	Uniform	No	CRC	NCI CTC and TNSc	Development of grade 2-4 chronic neuropathy	150 (71)	Mixed	No	Pre-existing neuropathy excluded	Yes	Yes	Yes (log additive and dominant)	Yes
Won (2011)	Oxaliplatin	GWAS	Korea	'homogenous'	Uniform	No	CRC	NCI CTC	Development of grade 2 for >7 days or grade 3	Exploratory 96 (39); validation 247 (85)	NS	Yes	Excluded all pre-existing PN	Yes	Yes	Unclear	Yes
Zarate (2010)	Oxaliplatin	*GSTM1, GSTT1, ERCC1 C118T, UGT1A1* promoter region polymorphism, *TYMs* 28bp repeats	Spain	NS	NS	No	CRC	NCI CTC	Development of grade 2-3	60	Uniform	No	No	Yes	Yes	Unclear	No

Table 3.5. Included cisplatin- based studies for systematic review of pharmacogenetics of CIPN

First author (Year)	Index drug(s)	SNPs investigated (those underlined highlight statistically significant associations)	Country	Ethnicity	Ethnicity uniform, mixed- adjusted for or mixed	Test for population substructure	Primary tumour	Assessment tool for CIPN	CIPN endpoints investigated	Sample size (number of 'cases' according to the authors definition)	Schedule/ dose uniform, adjusted for or mixed	Minimum dose for controls	Potential clinical confounders accounted for	HWE checked	Genotype QC measures described	Mode of inheritance used in analysis stated	Multiple testing adjustment
Alberola (2004)	Cisplatin	*MTHFR C677T*	Spain	NS	NS	No	Lung	WHO score	Development of grade 3-4 neuropathy	208 (8)	Uniform	Yes	No	NS	NS	Unclear	Single SNP
Fung (2012)	Cisplatin	90 SNPs in *GSTP1, COMT, TPMT*	Italy	Mixed (White, Asian, Other)	Mixed adjusted	No	Testicular	Michigan neuropathy screening instrument	MNSI score >1	66 (25)	Adjusted	No but cum dose adjusted for	No	Yes	'previously reported'	Different modes reported	Yes
Goekkhurt (2009)	Cisplatin	*GSTP1 Ile105Val, GSTM1, GSTT1, ERCC1 (C118T, C8092A), XPD (Lys751Gln, Asp312Asn), XRCC1 Arg399Gln, XPA A23G, TS (1494del6, VNTR 28bp repeat, VNTR +G/C SNP), MTHFR (C677T, A1298C), MTR*	Germany and Switzerland	NS	NS	No	Upper GI	NCI CTC	Development of grade 3-4	Cisplatin arm: 63 (12-15)	Adjusted and cisplatin and oxaliplatin groups analysed separately	No	Excluded those with PN> grade 1	NS	NS	Unclear	No

		A2756G, OPRT Gly213Ala															
Khrunin (2009)	Cisplatin	*GSTP1 (Ile105Val, Ala114Val), GSTM1, GSTT1, GSTA1 (rs3957357), GSTM3 (rs1799735, rs7483), ERCC1 (C118T, rs3212986), XPD (Asp312Asn, Lys751Gln), XRCC1 (arg194Trp, Arg280His, Arg399Gln), TP53 (rs17878362, rs1042522, rs1625895), CYP2E1 (96bp ins, rs2031920, rs6413432, rs2070676)*	Russia	Eastern Slavonic	Uniform	No	Ovarian	NCI CTC	Development of grade 2-3	95 (31)	Uniform	No	Diabetes excluded	Yes	NS	Unclear	Yes
Xu (2012)	Cisplatin	20 SNPs in *CTR1* gene	China	Han Chinese	Uniform	No	Lung	NCI CTC	Development of grade 1-3	204 (126)	Uniform cisplatin different concurrent drug (some neurotoxic)	Yes	No	Yes	NS	Evident in results (dominant)	Yes

Table 3.6. Included taxane studies for systematic review of pharmacogenetics of CIPN

First author (Year)	Index drug(s)	SNPs investigated (those underlined highlight statistically significant associations)	Country	Ethnicity	Ethnicity uniform, mixed-adjusted for or mixed	Test for population substructure	Primary tumour	Assessment tool for CIPN	CIPN endpoints investigated	Sample size (number of 'cases' according to the authors definition)	Schedule/ dose uniform, adjusted for or mixed	Minimum dose for controls	Potential clinical confounders accounted for	HWE checked	Genotype QC measures described	Mode of inheritance used in analysis stated	Multiple testing adjustment
Docetaxel studies																	
Eckhoff (2015)	Docetaxel	*GSTP1 (Ile 105Val, Ala114Val), ABCB1 (G2677T, C1236T, C3435T), TUBB2A (rs909964, rs909965, rs9501929, rs3734492, rs 13219681), NAT2 (rs1799931), ERCC1 (rs3212986), APT7A (rs2227291), CYP3A5 (*3), CYP3A4*1B, CHST3 (rs4148950, rs1871450), SLCO1B3 (rs11045585), SLC10A2 (rs2301159)*	Denmark	Western European	Uniform	No	Breast	NCI CTC	Development of grade 2-4	150 (75)	Adjusted	Minimum one dose only	Excluded pre-existing PN and accounted for DM and alcohol	Yes	Yes	Evident in results	No
Marsh (2007)	Docetaxel (with carboplatin)	27 SNPs in 16 genes including *ABCB1, ABCC 1and 2, ABCG2,*	UK	NS	NS	No	Ovarian	NCI CTC	Development of grade 2-4	266-296 in discovery set (57)	Uniform, paclitaxel and	No	Excluded those with PN> grade 1	Yes	NS	Unclear	Yes

		CYP1B1, CYP2C8, CYP3A4, CYP3A5, ERCC1, XPD, GSTP1 and *XRCC1*									docetaxel cohorts analysed separately						
Mir (2009)	Docetaxel	*GSTP1 (Ile105Val and Ala114Val), GSTM1, GSTT1*	France	NS	NS	No	Breast, lung, prostate and other	NCI CTC	Development of grade 2-4	58 (10)	Uniform	No	No	NS	Yes	Evident in results (dominant)	No
Sissung (2008)	Docetaxel	*ABCB1 C1236T, G2677T/A, C3435T*	USA	NS	NS	No	Prostate	NCI CTC	Probability of development CIPN during docetaxel therapy as a function of time	23 (NS)	Uniform	Uses time in outcome	No	Yes	NS	Unclear	No
Paclitaxel studies																	
Abraham (2014)	Paclitaxel	GWAS (selected SNPs published incl *rs3213619, rs2032582, rs1045642 (ABCB1), rs9501929 (TUBB2A), CYP2C8*4, rs8187710 and rs17222723 (ABCC2), CYP1B1*3, rs 301927 (EPHA6), rs3829306 (SLCO1B1*	UK	European	Uniform	Yes	Breast	NCI CTC	Development of grade 2-4 neuropathy Cumulative dose at grade2	1335 (360)	Uniform	Dose used in outcome	No	Yes	Yes	Unclear	Yes
Apellaniz-Ruiz (2015)	Paclitaxel	Whole exome sequencing *CYP3A4*	Spain	NS	NS	No	Breast and ovary	NCI CTC	NCI grade, development of grade 3 neuropathy, treatment modifications due to neuropathy	236	Mixed regimens	Cumulative dose adjusted for	Pre-existing PN excluded and effect of DM and alcohol examined	No	Yes	Yes	No
Baldwin (2012) Exploratory cohort European replication set African American	Paclitaxel	GWAS	USA	Mixed	Analysed in ethnically uniform cohorts	Yes	Breast	NCI CTC	Cumulative dose at grade 2 Maximum observed grade of neuropathy	855 (206) 154 (21) 117 (33)	Uniform	Dose used in outcome	No	NS	GWAS	Evident in results (uses a mixture of additive, dominant and recessive)	Yes
Bergmann (2012)	Paclitaxel	*CYP2C8 (*3, rs1058930, rs7909236, rs17110453), CYP3A4*1B, SLCOB3 (rs 60140950, rs7311358), ABCB1 (C1236T, G2677T/A, C3435T, rs9282564, rs2229109, rs2214102), CYP1B1 (rs1056836), CYP3A5 rs776746, ABCC1 Rs 504348, ABCC10*	Denmark and Sweden	Scandanavian	Uniform	No	Ovarian	NCI CTC	Time to increase of NCI CTC grading to 2 points above baseline NS	92(75 any grade, 17 grade 3)	Uniform	No. Time used in outcome	No	Yes	NS	Yes (additive)	No

		rs2125739, ABCC2 (rs 17222723, rs8187710, rs2273697), ABCG2 (rs2231142, rs2231137)															
Bergmann (2011)	Paclitaxel	CYP2C8*3, ABCB1 (C1236T, G2677T/A, C3435T), and exploratory analysis in SNPs in CYP3A5, ABCC1, ABCC2, ABCG2, ABCC10, CYP1B1 and SLCOB3.	Denmark and Sweden	Scandanavian	Uniform	No	Ovarian	NCI CTC	Time to increase of NCI CTC grading to 2 points above baseline	119 (81 any grade, 3 grade 3)	Uniform	No. Time used in outcome	Excluded pts with PN> grade 2	Yes	NS	Yes (additive)	No
Bergmann (2012)	Paclitaxel	GWAS	Scandan-avian cohorts	Caucasian	Uniform	No	Ovarian	NS	Development of grade 2-4 and time to neuropathy	239 (65)	Uniform	No. One outcome used time to event analysis	No	Yes	NS	Evident in results (recessive)	No
Beutler (2014)	Paclitaxel	49 Charcot Marie Tooth genes examined	USA	Mixed	Mixed	No	Breast, ovarian, lung, H&N, uterine and 'other'	Rate of change in EORTC CIPN20	Rapid increase in CIPN20 score versus slow progression of CIPN20 scores	119 (73)	Mixed regimens	Minimum no. of questionnaires but small	Pre-existing neuropathy excluded and diabetes status recorded	Yes	Yes	Unclear (evidently dominant from validation paper)	Yes
Boora (2015)	Paclitaxel/ carboplatin	*ARHGEF10 (rs9567362, rs2294039, rs17683288)*	USA	Mixed	Mixed	No	Ovarian, lung, uterinel, breast, H&N	Rate of change in EORTC CIPN20 scores	Rapid increase in CIPN20 score versus slow progression of CIPN20 scores	75 (47)	Small variability in paclitaxel dose, uniform schedule	Minimum no. of questionnaires thereby at least 3 cycles	Excluded pre-existing neuropathy	Yes	No but QC in place	Dominant	No
Boso (2014)	Paclitaxel	*ABCB1 (C3435T, C1236T, G2677A/T), ABCC2 (rs17222723, rs2804402, rs3740066, rs8187710), ABCG2(rs2622604) CYP1B1*3, CYP2C8 (*2, *3, *4, HapC, rs1341164, rs1934951), CYP3A4 (*1B, *16), CYP3A5 (rs776746), ERCC1 (Asn118Asn, Gln504Lys), ERCC2 (Lys751Gln, Asp288Asn), GSTM3 (rs1799735), GSTP1 (Ala114Val, Ile105Val, rs8191439), XRCC1 (Gln399Arg, XPC (Gln902Lys), MTHFR (Glu429Ala,*	Spain	Caucasian	Uniform	No	Breast	NCI CTC	Development of grade 2-4 neuropathy	43 (13)	Uniform	No	No	Yes	Yes	Dominant	No but lower p value to reflect exploratory nature

		Ala222Val), Also SNPs in RRM1, NOS3, NQO1, SOD2, TP53 UGT1A1 (rs10929302, rs4124874, rs4148323), UGT1A9 (rs7586110, rs17868323), and CBR3															
Chang (2009)	Paclitaxel	*ABCB1 (G2677T/A, C3435T)*	Korea	NS	NS	No	Breast	NCI CTC	Development of grade 3-4	108 (12)	Uniform	No	Excluded pre-existing PN > grade 1	NS	NS	Unclear	No
de Graan (2013)	Paclitaxel	*CYP3A4*22, CYP2C8*3, CYP2C8*4, ABCB1 C3435T*	Netherlands	Mixed	NS	No	Breast, ovarian, UGI, lung, H&N, CUP	NCI CTC	Development of any grade, severity and grade 3	Exploratory 261 (2 grade 3; 20 grade 2 or greater; 106 any grade); validation 239 (113 any grade)	Adjusted	Time used in outcome	No	Yes	NS	For CYP3A4*22 evident in results (dominant)	No
Green 2008	Paclitaxel	*CYP2C8 (*1B, *1C, *2, *3, *4, *5, *6, *7, *8 and P404A), ABCB1 (G2677T/A and C3435T), CYP3A4*1B*	Sweden	Caucasian	Uniform	No	Ovarian	NCI CTC	Development of grade 1-2	33 (NS)	Mixed dose not schedule	Yes	No	Yes	NS	No assumption for CYP3A5, dominant for CYP2C8	No
Green 2011	Paclitaxel	*CYP2C8-HapC, CYP3A5*3*	Sweden	Caucasian	Uniform	No	Ovarian	Neurotoxicity scale (N score)	?any grade- not clear	33 (12)	Mixed dose not schedule	Yes	No	NS	NS	Unclear	No
Hasmats (2012)	Paclitaxel	Initially 123 SNPs in candidate toxicity genes with 11 finally selected	Spain and Sweden-	NS	NS	No	Breast, ovarian, lung, CUP	NCI CTC	Cumulative dose at grade 2 neuropathy	94 (NS)	Mixed	Cum. dose used in outcome	No	NS	Yes	Unclear	No
Hertz (2012)	Paclitaxel	*CYP1B1*3, CYP2C8*3, CYP3A4 *1B, CYP3A5*3C, ABCB1*2*	USA	White and African American and other	Mixed adjusted	No	Breast	NCI CTC	Development of grade 3-4	109 (12)	Mixed	No	No	Yes	Yes	Yes	Yes
Hertz (2013)	Paclitaxel	*CYP2C8*3*	USA	White and African American	Analysed in ethnically uniform cohorts	No	Breast	NCI CTC	Cumulative dose at grade 2 neuropathy	411 in three sets; A European American set 209 pts; An African American set 107 pts and a combined mixed race group total 411 (76)	Mixed	No. Cumulative dose used in outcome	No	Yes	NS	Yes	Single outcome
Hertz (2014)	Paclitaxel	*CYP2C8 *2* and *4 plus 1275 SNPs including *rs492338* in	USA	White and 'Non-Caucasian	Analysed in a uniform caucasian and a mixed	Yes	Breast	NCI CTC	Development of grade 2-4 neuropathy and cumulative	288 (49) in Caucasian cohort and 124 (28) in	Mixed	No. Cumulative dose	No	Yes	Yes	Yes (dominant for CYP2C8 variants, no	Yes

		ABCG2 (significant in Caucasian cohort)			'non-caucasian' cohort				dose at grade 2 neuropathy	non-Caucasian cohort		used in outcome				assumption evident for the remainder)	
Hu (2016)	Paclitaxel with carboplatin	CYP3A5*3	China	Chinese	Uniform	No	Ovarian	NCI CTC	Not pre-stated. From results development of any grade neuropathy	75 (30)	Uniform	Yes	No	No	No	NA (only 2 genotypes in cohort)	No (single SNP)
Kulkarni (2014)	Paclitaxel	*RWDD3 (rs2296308)* and *TECTA (rs1829)*	USA	Mixed	mixed	No	Breast, ovarian, lung, H&N, others	Rate of change of EORTC CIPN20 score	Rapid change in CIPN20 score versus slow progression of CIPN20 score	119 (73)	Mixed	Minimum no. of questionn aires but small	Pre-existing neuropathy excluded	Yes	Yes	Dominant and additive	No
Lambrechts	Paclitaxel/ carboplatin	26 SNPs in 18 genes *ABCB1 (C1236T, C3435T, G1199A), ABCC1(rs2230671, rs2074087), ABCC2 (rs2073337, rs12762549), ABCG2 (rs2231142), ABCA1 (rs363717), SCLO1B3 (rs4149117, rs11045585), CYP1B1 (rs1056836), CYP3A4 (rs2740574), CYP3A5 (rs776746), TP53 (rs1042522), MAPT (rs11568305), GSTP1 (Ilw105Val, Ala114Ala), ERCC1 (rs11615, rs3212961), ERCC2 (Asp312Asn), SLC12A6 (rs7164902), SERPINB2 (rs6104), PPARD (rs2076169), ICAM1 (rs1799969)*	Belgium and luxembur g	Mixed	Mixed	No	Ovarian	NCI CTC	Appears to be any grade but not clearly specified	265 (48 grade 2-3)	Unclear	Yes	Pre-existing neuropathy excluded	Yes	Yes	Additive	Yes
Leandro- Garcia (2013)	Paclitaxel	GWAS	Spain and Sweden	Caucasian	Uniform	No	Breast, ovarian, lung	NCI CTC	Cumulative dose at grade 2 neuropathy	144 (69)	Uniform	Dose used in outcome	Excluded pre-existing PN	Yes	Yes	Yes (additive)	Yes
Lee (2014)	Paclitaxel	*ABCB1 (G2677T/A, C3435T, rs1128503), CYP1B1 (rs1056836), CYP2C8*5, CYP3A4*18, CYP3A5*3* and a group of SNPs selected for putative gemcitabine effects (including *RRM1*)	Korea	Korean	Uniform	No	Breast	NS	Appears to be any grade but not specifically stated	85 (NS)	Uniform	NS	No	NS	Yes	Evident in results (dominant)	Yes
Marsh (2007)	paclitaxel (with carboplatin)	27 SNPs in 16 genes including *ABCB1, ABCC 1and 2, ABCG2, CYP1B1, CYP2C8, CYP3A4, CYP3A5,*	UK	NS	NS	No	Ovarian	NCI CTC	Development of grade 2-4	Paclitaxel 266-296 in discovery set (147)	Uniform, paclitaxel and docetaxel	No	Excluded those with PN> grade 1	Yes	NS	Unclear	Yes

		ERCC1, XPD, GSTP1 and *XRCC1*									analysed separately						
Ofverholm (2010)	Paclitaxel	*CYP2C8*3, CYP3A4*1b, ABCB1 (G2667T/A, C3435T)*	Sweden	NS	NS	No	Breast and ovarian	NCI CTC	All patients recruited as they had grade 1-2 neuropathy	36	Mixed	Controls did not receive paclitaxel	Cases selected when they developed PN	Yes	NS	Unclear	No
Park (2014)	Paclitaxel	*GSH3 (rs6438552), MAPT (haplotype 1, rs242557)*	Australia	NS	NS	No	Mixed (mainly breast)	NCI CTC and NCS	Development of grade 2/3 neuropathy and NCS outcomes	21 (7)	Mixed	No	Excluded all pre-exicting PN and causative conditions for PN	NS	NS	NS	No
Sissung (2006)	Paclitaxel	*ABCB1 G2677T* and *C3435T*	Germany	NS	NS	No	Solid tumours	PNP score	Development of any neuropathy	22 (NS)	Mixed (duration of infusion only variable)	Uses time in outcome	PNP score >3 prior to therapy excluded	NS	NS	Unclear	No
Sucheston (2011)	Paclitaxel	20 and 9 SNPs in *FANCD2* and 17 and 12 SNPs in *BRCA1*	USA	Mixed	Mixed adjusted	Yes	Breast	NCI CTC	Development of grade 3-4	888 (107)	Mixed	No	No	Yes	Yes	Yes (Additive and dominant depending of MAF)	Yes
Combined taxane cohorts (paclitaxel and docetaxel analysed together)																	
Kim (2009)	Paclitaxel and docetaxel with paclitaxel or carboplatin	*GSTP1 Ile105Val, GSTM1, GSTT1, ERCC1 (C118T, C8092A), XPD Lys751Gln, XRCC1 (Arg399Gln, Arg194Trp), ABCB1 (C3435T, G2677T/A)*	Korea	Korean	Uniform	No	Ovarian	NCI CTC	Development of grade 3-4	118 (18)	Mixed	No	No	NS	NS	Evident in results (at least some appear dominant)	No
McWhinney-Glass (2013)	Paclitaxel and docetaxel (with carboplatin)	1261 SNPs in 60 genes incl *SOX10, BCL2, OPRM1, TRPV1*	UK	NS	NS	Yes	Ovarian	NCI CTC	Development of grade 2-4	Exploratory 404 (91); validation 404 (91)	Adjusted	Yes	Excluded all pre-existing PN		NS	Yes	Yes
Rizzo (2010)	Taxanes	*CYP2C8 (*1, *2, *3* and **4), CYP1B1 (*1* and **3), ABCB! (C1236T, G2677T/A, C3435T)*	Italy	Caucasian	Uniform	No	Breast	NCI CTC	Development of any neuropathy	86 (7)	Mixed	No	No	Yes	NS	Unclear	Yes

Table 3.7. Included vincristine-based studies for systematic review of pharmacogenetics of CIPN

First author (Year)	Index drug(s)	SNPs investigated (those underlined highlight statistically significant associations)	Country	Ethnicity	Ethnicity uniform, mixed-adjusted for or mixed	Test for population substructure	Primary tumour	Assessment tool for CIPN	CIPN endpoints investigated	Sample size (number of 'cases' according to the authors definition)	Schedule/ dose uniform, adjusted for or mixed	Minimum dose for controls	Potential clinical confounders accounted for	HWE checked	Genotype QC measures described	Mode of inheritance used in analysis stated	Multiple testing adjustment
Aplenc (2003)	Vincristine	*CYP3A4*1B, CYP3A5 (*3* and *6)	Mainly USA	Mixed (White, African American and Other)	Mixed	No	ALL	CCG criteria	Development of grade 3-4 neuropathy	533 (27/28)	NS	No (but ALL study so early stopping less likely)	No	Yes	NS	Yes (dominant)	Yes
Broyl (2010)	Vincristine	3404 SNPs incl multiple SNPs found to be associated	Netherlands, Germany and Belgium	NS	NS	No	Myeloma	NCI CTC	Development of grade 2-4 neuropathy	183 (11 early onset, 17 late onset)	Uniform	Yes	Excluded those with >2 PN	NS	NS	Unclear	Yes
Cho (2010)	Vincristine	*GSTP1 Ile105Val, GSTT1, GSTM1*	Korea	Korean	Uniform	No	DLBCL	NCI CTC	Development grade 3-4	94 (2)	Uniform	No	No	Yes	NS	Evident from results (dominant)	No
Diouf (2015)	Vincristine	GWAS	USA	Mixed	Mixed	Yes	ALL	NCI CTC (or a similar modified version)	Development of grade 2-4 neuropathy	222 (64) in one cohort 99(22) in a second	Adjusted	Yes	NS	NS	Yes	NS, evidently recessive for the significant SNP	Yes
Egbelakin (2011)	Vincristine	*CYP3A5 *3, *6, *7*	USA	Mixed	NS	No	ALL	NCI CTC	looks at a number of different outcomes *	107 (105 any grade, 57 grade 3)	Uniform	Time used in outcome	Excluded those with PN> grade 1	NS	NS	Yes (recessive)	No
Guilhaumou (2011)	Vincristine	*CYP3A4, CYP3A5, ABCB1* (SNPs not specified)	France	Caucasian	Uniform	No	Paediatric solid tumours	Global toxicity score	Global toxicity score greater or equal to 3	24 (8)	Uniform	No	No	NS	NS	Unclear	No
Gutierrez-Camino (2016)	Vincristine	*CEP72 (rs924607)*	Spain	Spanish of European background	Uniform	No	ALL	NCI CTC	Development of grade 2-4 neuropathy during induction phase	142 (36)	Uniform	Yes	No	NS	NS	Yes. Recessive	Single outcome
Kim (2008)	vincristine 1.4mg/m2 max 2mg	*ABCG2 Q141K, V12M*	Korea	Korean	Uniform	No	DLBCL	NCI CTC	Development of any grade and grade 3-4	145 (6 grade 3-4)	Uniform	No	No	Yes	NS	Evident in results (dominant)	No
Kishi (2007)	Vincristine	*CYP3A5*3, CYP3A4*1B, GSTP1 Ile105Val, GSTM1, GSTT1, ABCB1 (G2677T/A, C3435T), MTHFR (C677T, A1298C), NR3C1 A1088G, SLC1 9A1 80A>G, TPMT (G238C, G460A, A719G), TYMS enhancer repeat, UGT1A1 promoter*	USA	Mixed	Mixed adjusted	Yes	ALL	NCI CTC	Development of grade 2-4	233 (44)		No	No	Yes	NS	Evident in results (mixed)	Yes

		repeat, VDR intron 8G>A and Fok1															
Moore (2011)	vincristine	*CYP3A5*3 and *6*	Australia	Mixed (White 90%, Pacific Islander, Aboriginal, Asian)	NS	No	Leukaemia, lymphoma, CNS and other	NCI CTC	Development of grade 3-4	43 (6)	Uniform		No	Yes	NS	Unclear	No
Sepe (2012)	Vincristine	*GSTP1 Ile105Val, GSTM1, GSTT1, MTHFR C677T, TS 28bp ins, UGT1A1 TA ins, TMPT (416 and 719)* plus unspecified SNPs in *CYP3A4* and *CYP 3A5*	USA	Mixed (White, Black NOS, Asian, Hispanic, Other)	Mixed adjusted	No	ALL	CCG toxicity grading	Development of any neuropathy	557 (23)	Uniform	No (but ALL and unlikely to be much variation)	No	Yes	Yes	Unclear	Yes

Table 3.8. Included miscellaneous studies for systematic review of pharmacogenetics of CIPN

First author (Year)	Index drug(s)	SNPs investigated (those underlined highlight statistically significant associations)	Country	Ethnicity	Ethnicity uniform, mixed-adjusted for or mixed	Test for population substructure	Primary tumour	Assessment tool for CIPN	CIPN endpoints investigated	Sample size (number of 'cases' according to the authors definition)	Schedule/ dose uniform, adjusted for or mixed	Minimum dose for controls	Potential clinical confounders accounted for	HWE checked	Genotype QC measures described	Mode of inheritance used in analysis stated	Multiple testing adjustment
Single drugs only studied by one group																	
Ekhart (2008)	Carboplatin	*CYP2B6 (C64T, C1459T, A785G, G516T), CYP2C9 (*2,*3), CYP2C19*2, CYP3A4 (*1B, *3), CYP3A5 (*2, *3), GSTA (C-69T, G-52A), GSTP1 (Ile105Val, Ala114Val), ALH1A1*2, ALDH3A1*2*	Netherlands	Caucasian	Uniform	No	Breast, ovarian and germ cell	NCI CTC	Development of grade 2-3	113 (8)	Adjusted	No	No	NS	NS	Unclear	No
Fountzilas (2013)	Ixabepilone	*ABCB1 (C2677T, C1236T, C3435T), CYP3A4*16, CYP2C8 rs1152080*	Greece	NS	NS	No	Breast	NS	NS	64 (12 grade 3, 48 any grade)	NS	No	Excluded those with PN> grade 1	NS	NS	Unclear	No
Mixed cohorts of differentially neurotoxic platinums																	
Brouwers (2009)	**Oxaliplatin** or **cisplatin**	*GSTP1 (Ile105Val), GSTM1, GSTT1*	Netherlands	NS	NS	No	CRCl, lung, testicular, yolk sac and H&N	Questionnaire, neurological and vibration tests	vibration testing abnormalities	45 (26)	NS	Yes	No	Yes	NS	Unclear	No
Joerger (2012)	**Cisplatin** and carboplatin	24 SNPs in 15 genes including *ERCC1, GSTP1, GSTM1, RRM1, XRCC1, XRCC3, XPD10, XPD23, REQ1, CDK, SLC28A1/2, RAD54L, DCK.*	Netherlands	Mixed (White 95%, Black, Asian, Other)	Mixed	No	Lung	NCI CTC	Development of 'severe PNP' (not defined)	137 (7)	Mixed	No	No	NS	NS	Unclear	No
Xu (2012)	**Cisplatin** OR Carboplatin	22 SNPs in *eIF3*	China	Han Chinese	Uniform	No	Lung	NCI CTC	Development of grade 2-3	282 (111)	Uniform cisplatin but different concurrent drug (some neurotoxic)	No	Diabetes excluded	NS	NS	Unclear	Yes
Mixed study cohorts with more than one high-risk neurotoxic drug																	
Fung (2012)	**Cisplatin** but some patients received concuurent **vinblastine**	90 SNPs in *GSTP1, COMT, TPMT*	Italy	Mixed (White, Asian, Other)	Mixed adjusted	No	Testicular	Michigan neuropathy screening instrument	MNSI score >1	66 (25)	Adjusted	No but cum dose adjusted for	No	Yes	'previously reported'	Different modes reported	Yes
Isla (2004)	**Docetax**el AND **cisplatin**	*ABCB1 C3435T, ERCC1 C118T, XPD (Lys751Gln,*	Spain	NS	NS	No	Lung	WHO	Development of grade 2-4	62 (26-39)	Uniform	No	No	Yes	Yes	Unclear	No

		Asp312Asn), RRM1 -37C/A,															
Johnson (2015)	**Cisplatin** Or carboplatin (some with **paclitaxel**)	174 SNPs across 43 genes including *GSTP1 Val114Ala, ERCC1 Gln504Lys, ERCC2 (Lys751Gln, rs 1799787, rs238415, rs50871)and SNPs in ABCC1, 2,3 and **ABCC4,** XRCC1, RRM1, MGMT**,** GPX2,3,5 and 6 and **GPX7**. APEX1, CD3EAP, CYP2C9, GCLC, GCLM, GSR, GSS, GSTA2,3,4 and 5, GSTM2,4 and 5, GSTO 1 and 2, GSTZ1, MSH 2, 3 and 6, OGG1, RAD50,51,52 and 54B, XPA, XPC.*	USA	Caucasian	Uniform	No	Lung	NCI CTC	Development of CIPN	400 (141)	Mixed	No	Excluded pre-existing PN and DM	Yes	Yes	Additive	Yes
Lamba (2014)	**Cisplatin** OR carboplatin (some with **paclitaxe**l)	57 SNPs: full list not available in paper	USA	Caucasian	Uniform	No	NSCLC	NCI CTC	Appears to be development of grade 3-4 neuropathy	86 (5)	Mixed	Number of cycles adjusted for	No	Yes	Yes	Mulitple: dominant, co-dominant or additive	Yes
Leandro- Garcia (2012)	**Paclitaxel** with carboplatin or **cisplatin**	*TUBB2A -112 A>G, -157A>G, -101T>C*	Sweden and Spain	NS	NS	No	breast, ovarian, lung, bladder, urinary tract, GCT, H&N	NCI CTC	Cumulative dose at grade 2 neuropathy	214 (107)	NS	Dose used in outcome	No	Yes	Yes	Evident in results (dominant)	No
Leskela (2010)	**Paclitaxel** with carboplatin or **cisplatin**	*CYP2C8(*3, *4, HapC, *1B), CYP3A4*1B, CYP3A5*3, ABCB1 (G2677T, C1236T, C3435T, rs9282564), SLCO1B1 rs4149056, SLCO1B3 (rs4149117, rs7311358)*	Spain	Spanish	NS	No	Breast, Ovarian, Lung, uterus, peritoneal, H&N and GCT	NCI CTC	Cumulative dose at grade 2 neuropathy	118 (58)	Adjusted	Dose used in outcome	Excluded pre-existing PN	NS	Yes	Yes (additive)	No
Oldenburg (2007)	**Cisplatin** although almost half also had **vinblastine**	*GSTP1 Ile105Val, GSTM1, GSTT1*	Norway	Caucasian	Uniform	No	Testicular	Scale for Chemotherapy Induced Neurotoxicity (SCIN)	3 categories based on SCIN score as categorical variables	238 (116 any grade paraesthesia 58 'quite a bit- very much')	Adjusted	No but cumulative dose adjusted for	No	NS	NS	Evident in results (at least one recessive)	No
Xu (2012)	**Cisplatin** but some patients also received **vindesine** or **docetaxel**	20 SNPs in CTR1 gene	China	Han Chinese	Uniform	No	Lung	NCI CTC	Development of grade 1-3	204 (126)	Uniform cisplatin different concurrent drug (some neurotoxic)	Yes	No	Yes	NS	Evident in results (dominant)	Yes

Glutathione S-transferases

GSTP1

The *GSTP1 Ile105Val* SNP (rs1695) was the most commonly studied variant with 44 studies investigating a possible association with CIPN (82, 90, 94, 95, 98, 103, 215, 273, 274, 279, 291, 292, 294, 295, 297-300, 302-304, 306-309, 311-314, 316, 319, 320, 324, 325, 327, 329, 333, 338, 339, 341, 342, 344, 347, 348) Thirteen of these also examined the *Ala114Val* polymorphism in GSTP1 (90, 95, 103, 274, 294, 295, 297, 299, 304, 308, 329, 333, 342).

GSTP1 and platinums

27 studies investigated a link with oxaliplatin- induced peripheral neuropathy. Of these, four reported a significantly reduced risk in those patients demonstrating the AA phenotype (Ile/Ile) (307, 319, 325, 327), whilst a further study demonstrated a trend towards this outcome (302). In keeping with this, two studies found a significantly increased risk of neuropathy (306) or of discontinuing FOLFOX chemotherapy due to neuropathy (300) with the GG (Val/Val) genotype. In contradiction to these results, however, three studies found a significantly increased risk of neuropathy with the AA genotype (95, 320, 329) with a fourth study showing a trend towards this result (316). A total of 16 studies of *GSTP1 Ile105Val* showed no significant difference in the risk of neuropathy with oxaliplatin (90, 94, 273, 279, 294, 297, 303, 304, 309, 311-314, 325, 339, 348). Two studies including both oxaliplatin and cisplatin treated patients in a combined analysis showed an increased risk with the AA genotype (298) and no significant difference (215), respectively.

For cisplatin alone, one study demonstrated a significantly reduced risk of neuropathy with the GG genotype (338), a second showed the opposite effect (98) and two showed no significant difference (308, 347). A single carboplatin study showed no evidence of effect (333).

For oxaliplatin and GSTP1 Ile105Val, enough data was presented to allow meta-analysis. Of the 27 studies, 11 had to be excluded due to insufficient results available (215, 273, 294, 303, 304, 312-314, 325, 339, 348). Six studies (279, 298, 300, 309, 311, 327) could be included in association with development of NCI CTC grade 3-4 neuropathy, five studies were included for association with NCI CTC grade 2-4 neuropathy (90, 94, 297, 307, 319). Of the studies that utilised the oxaliplatin-specific scale, four studies could be included in respect to development of grade 3-4 neuropathy (302, 306, 320, 352) and three with grade 2-4 neuropathy (302, 316, 320). Two studies presented data for development of any grade neuropathy (279, 320). Overall meta-analysis of included studies showed no evidence of significant association (figure 3.2).

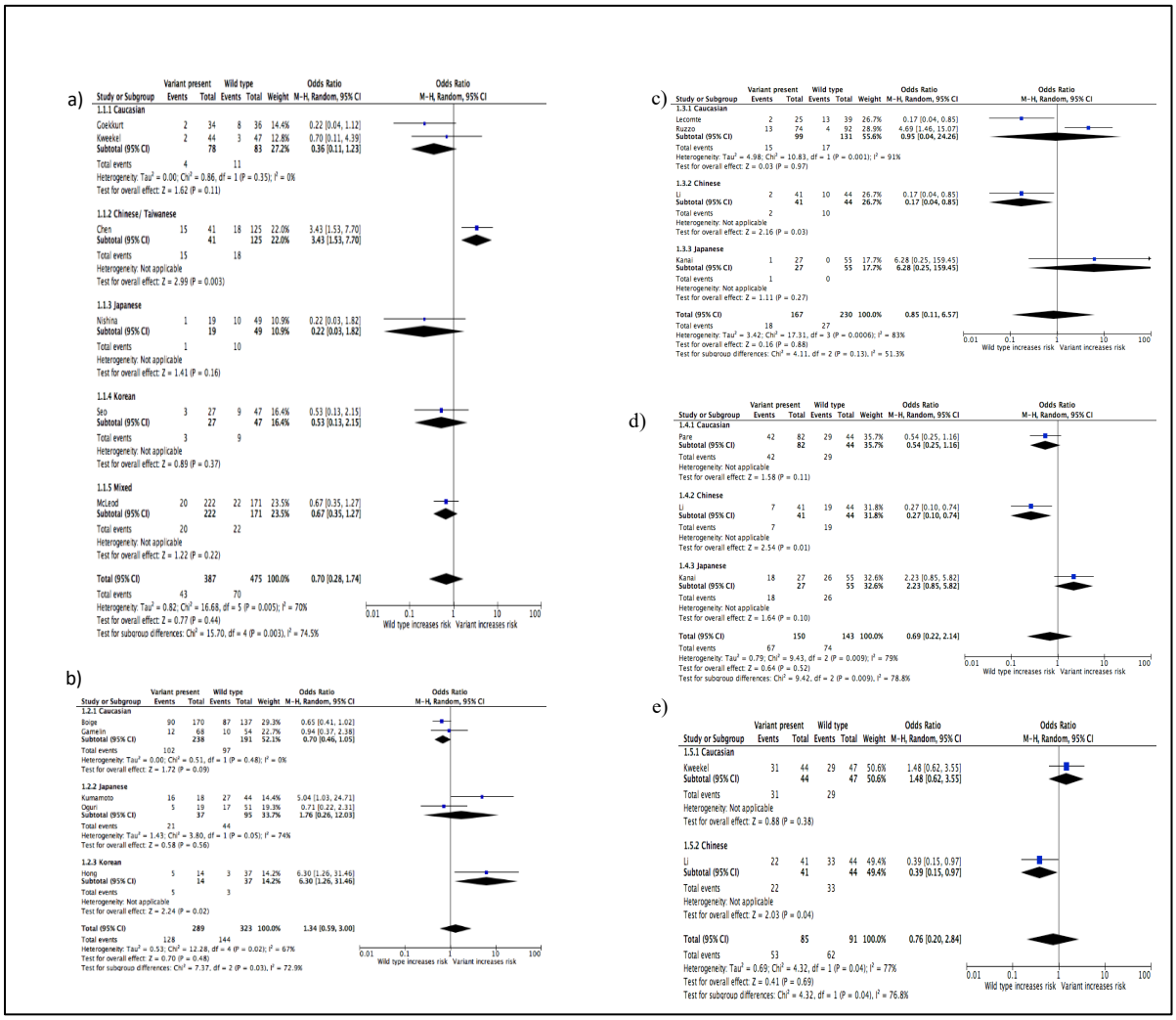


Figure 3.2. Forest plots demonstrating pooled odds ratios for included studies for association between GSTSP1 Ile105Val and oxaliplatin neuropathy a) NCI CTC grade 3-4 b) NCI CTC grade 2-4 c) oxaliplatin specific scale grade 3-4 and d) oxaliplatin specific scale grade 2-4 and e) any grade

GSTP1 and taxanes

Nine studies investigated *GSTP1 Ile105Val* and taxanes, but two of these involved the same population of patients (295, 299). Of these, one study showed an increased risk with the AA genotype (329) and in the other seven patient populations, no significant difference was seen (82, 103, 274, 295, 299, 341, 342, 344). One study reported an association between carrying a variant of *rs1138272* (Ala114Val) and development of grade 2 or greater peripheral neuropathy with docetaxel in a cohort of breast cancer patients (OR 3.82, 95%CI 1.34-11.09) (103). Only one study (329) presented their full results, therefore meta-analysis was not possible.

GSTP1 and vincristine

Three studies investigated *GSTP1* Ile105Val in vincristine-induced neuropathy but none demonstrated a significant association (291, 292, 324). Insufficient data was available to proceed to meta-analysis.

GSTM1

GSTM1 deletion and its impact on risk of neuropathy was investigated in 20 studies.

GSTM1 and platinums

Of 11 oxaliplatin studies (95, 297, 298, 300, 303, 304, 306, 309, 312, 319, 348), one reported *GSTM1* null subjects were more likely to develop $\geq$grade 2 CIPN (319). Four mixed platinum studies showed no effect of *GSTM1* deletion (98, 215, 298, 338). One cisplatin study showed a protective effect of the *GSTM1* null genotype (308) along with a reduced risk with certain *GSTM3* genotypes.

Sufficient data was presented in four oxaliplatin trials to include in the meta- analyses: two in association with development of NCI CTC grade 3-4 neuropathy (298, 309) and two in association with development of NCI CTC grade 2-4 (297, 319). No significant association was seen; OR 1.01 (95% CI 0.52-1.95, I^2=17%) and OR1.79 (95% CI 0.62-5.23, I^2=69%) for grade 3-4 and 2-4 neuropathy, respectively.

GSTM1 and taxanes

Two taxane based studies (329, 341) demonstrated no significant effect of *GSTM1* deletion on risk of neuropathy. Insufficient data was presented to allow meta-analysis.

GSTM1 and vincristine

Three vincristine (291, 292, 324) studies demonstrated no effect of *GSTM1* deletion. Insufficient data was presented to allow meta-analysis.

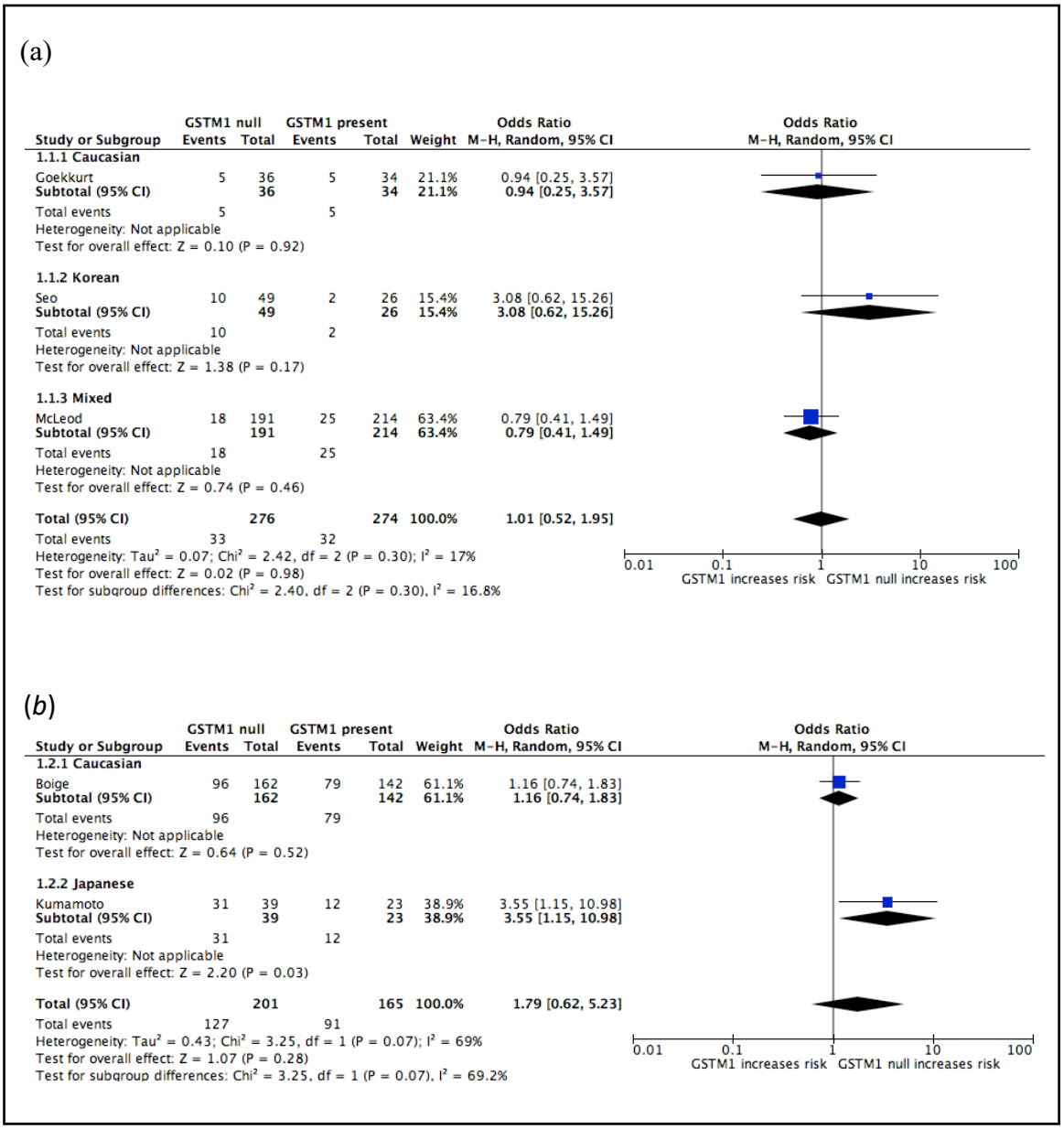


Figure 3.3. Forest plot for association between GSTM1 deletion and development of (a) NCI CTC grade 3-4 neuropathy (b) NCI CTC grade 2-4 neuropathy with oxaliplatin

GSTT1

19 studies using oxaliplatin (95, 297, 303, 304, 306, 309, 312, 319, 339, 348), oxaliplatin or cisplatin (215, 298), cisplatin (308, 338), taxanes (329), and vincristine (42, 43, 92) showed no effect of GSTT1 deletion on risk of neuropathy. Seven of the nine oxaliplatin studies (94, 95, 297, 298, 307, 309, 319) were suitable for meta-analysis with no statistically significant pooled effect demonstrated (OR 0.74, 95% CI 0.25-2.17, I^2=0% and OR 1.22, 95% CI 0.73-2.03, I^2=0% for NCI CTC grade 3-4 and 2-4 neuropathy, respectively) (figure 3.4).

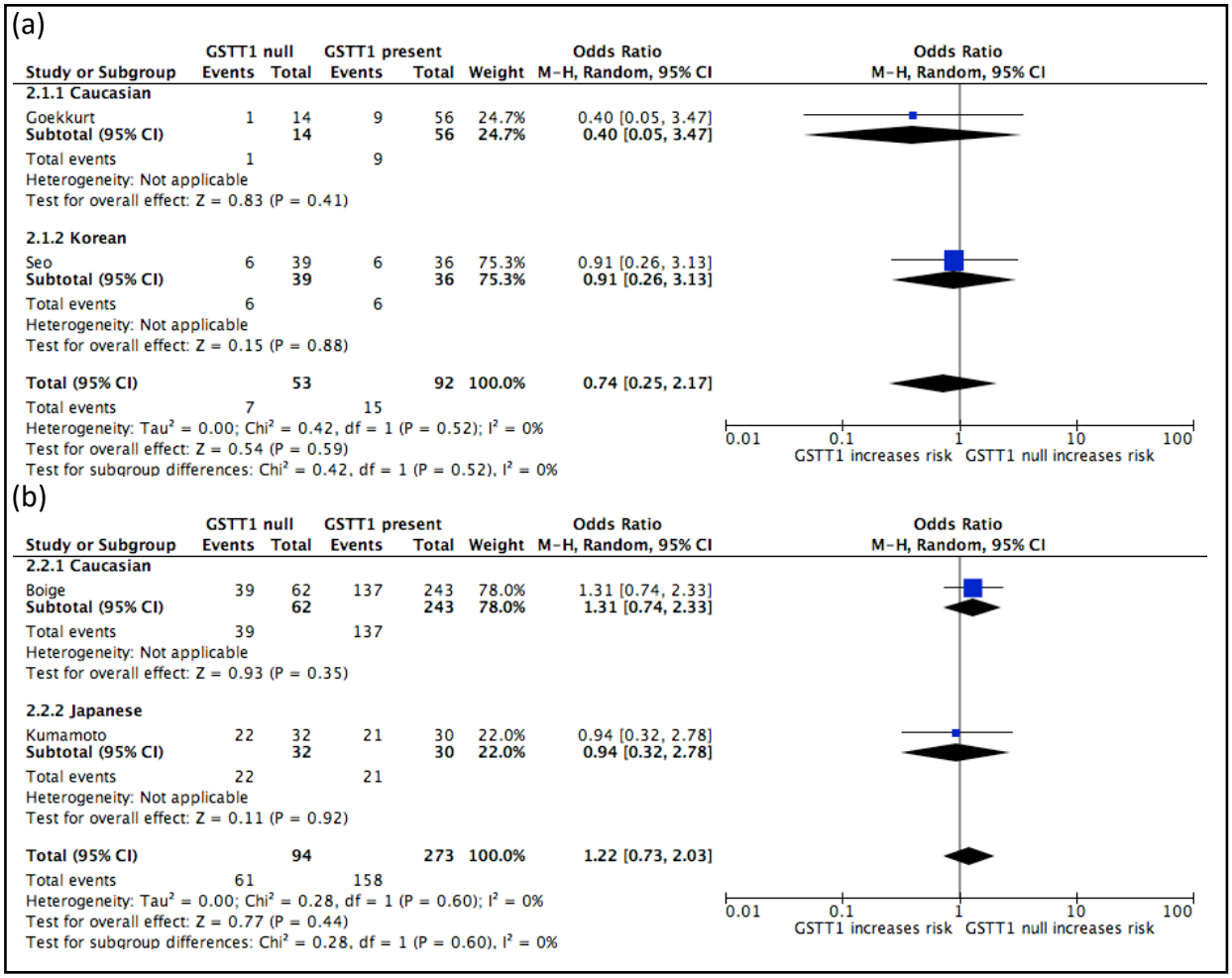


Figure 3.4. Forest plots for association between GSTT1 deletion and development of (a) NCI CTC grade 3-4 neuropathy and (b) NCI CTC grade 2-4 neuropathy with oxaliplatin

Excision Repair Cross Complementing (ERCC) genes

29 studies examined an association with *ERCC1. ERCC1* is implicated in platinum resistance and is therefore a biologically plausible target to examine with regard to platinum toxicity.

ERCC1

Platinum

One study demonstrated an association of the *ERCC1* C118T SNP with time to development of grade 1 chronic oxaliplatin- induced neuropathy (94). The other 20 studies investigated an association with oxaliplatin (94, 294, 297, 298, 300, 303, 304, 306, 307, 309, 311-314, 319, 325, 327, 332, 339, 348) while three investigating cisplatin or carboplatin (98, 298, 308) showed no statistically significant association with neuropathy.

Only six of the 20 oxaliplatin studies (297, 298, 300, 309, 319, 332) were eligible for inclusion in the meta-analysis, but no statistically significant association was shown (OR 0.87, 95% CI 0.47-1.62, I^2=0% and OR 1.22 0.77-1.95, I^2= 0% for C118T and NCI CTC grade 3-4 and 2-4, respectively, and OR 2.33, 95% CI 0.91-5.95, I^2= and OR 1.88, 95%CI 0.78-4.52 for C809A and NCI CTC grade 3-4 and 2-4 neuropathy, respectively).
Only six of the 20 oxaliplatin studies (297, 298, 300, 309, 319, 332) were eligible for inclusion in the meta-analysis, but no statistically significant association was shown (OR 0.87, 95% CI 0.47-1.62, I^2=0% and OR 1.22 0.77-1.95, I^2= 0% for C118T and NCI CTC grade 3-4 and 2-4, respectively, and OR 2.33, 95% CI 0.91-5.95, I^2= and OR 1.88, 95%CI 0.78-4.52 for C809A and NCI CTC grade 3-4 and 2-4 neuropathy, respectively).

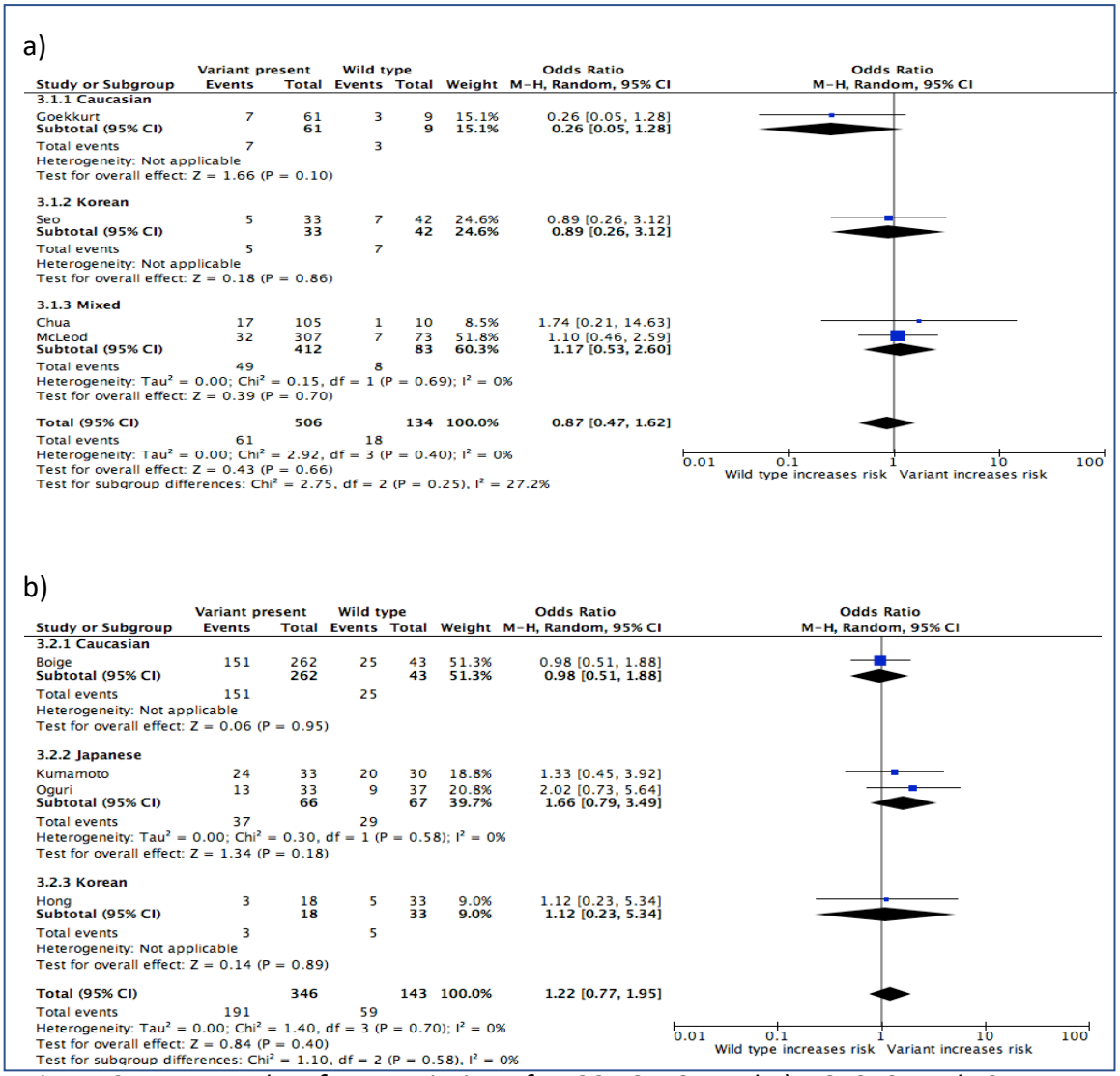


Figure 3.5. Forest plots for association of ERCC1 C118T and a) NCI CTC grade 3-4 neuropathy and b) NCI CTC grade 2-4 neuropathy with oxaliplatin

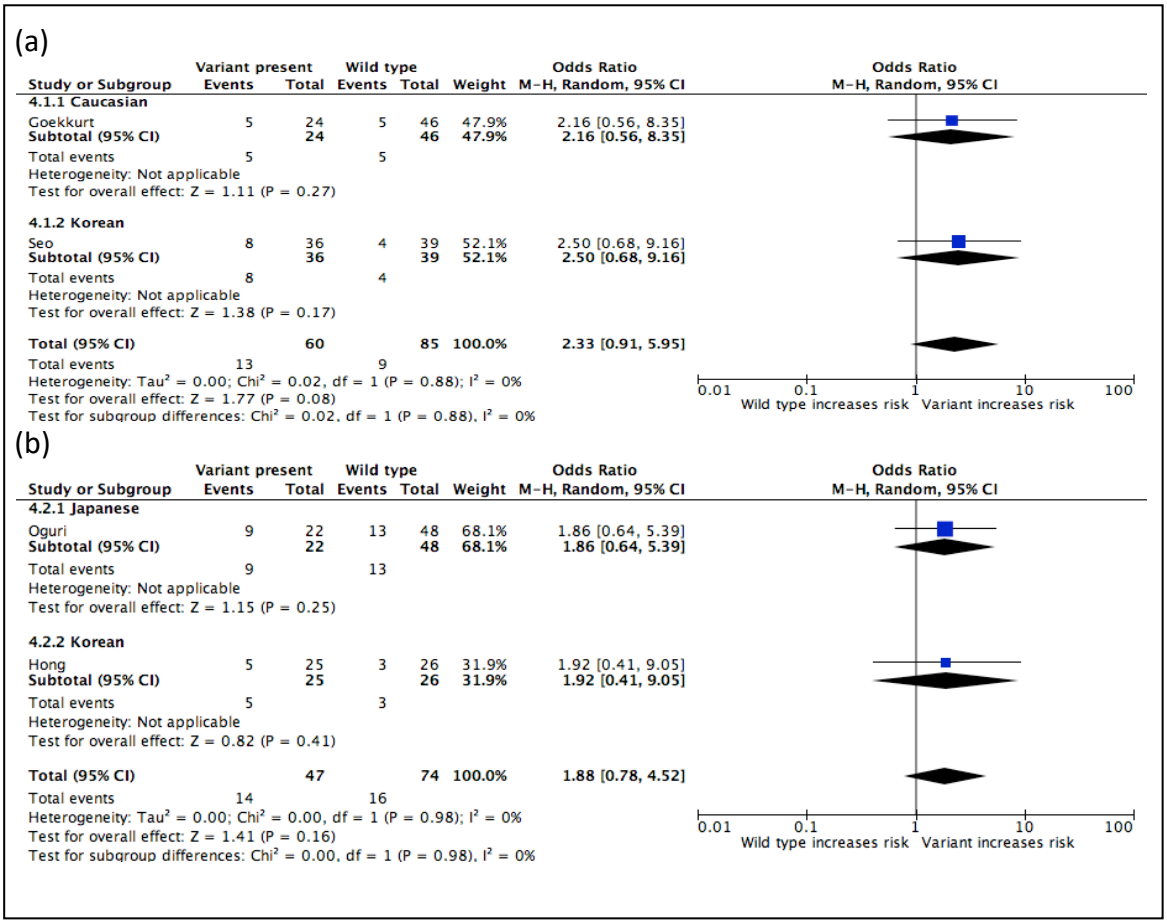


Figure 3.6. Forest plot for association between ERCC1 C809A and development of (a) NCI CTC grade 3-4 neuropathy and (b) NCI CTC grade 2-4 with oxaliplatin

Taxane/ taxane-platinum

One study initially showed an increased risk of developing grade 3-4 neuropathy with taxane- platinum combination treatment with the CC genotype of *ERCC1* C8092A on univariate analysis but significance was not maintained in a multivariate model (341). Three studies in two cohorts of taxane/platinum-treated patients (295, 299, 342) and one docetaxel study (103) showed no evidence of association. One study in 43 breast cancer patients treated with weekly paclitaxel demonstrated a significant association with carrying at least one variant allele at *rs3212986* (Gln504Lys) and development of grade 2-4 neuropathy (p 0.006)(344). These studies could not be combined in meta-analysis due to insufficient data presented.

ERCC2

Multiple SNPs in *ERCC2* were examined across 25 studies (98, 294, 295, 297-300, 303, 304, 306-308, 311-313, 317, 319, 325, 327, 331, 339, 341, 342, 344, 348) looking at platinum, platinum/taxane or taxane- treated patients. None showed an association with an increased risk of developing peripheral neuropathy either individually or in meta-analysis. A small number of oxaliplatin- based studies gave individual numbers involved and were able to be included in the meta-analysis (figures 3.7 and 3.8).

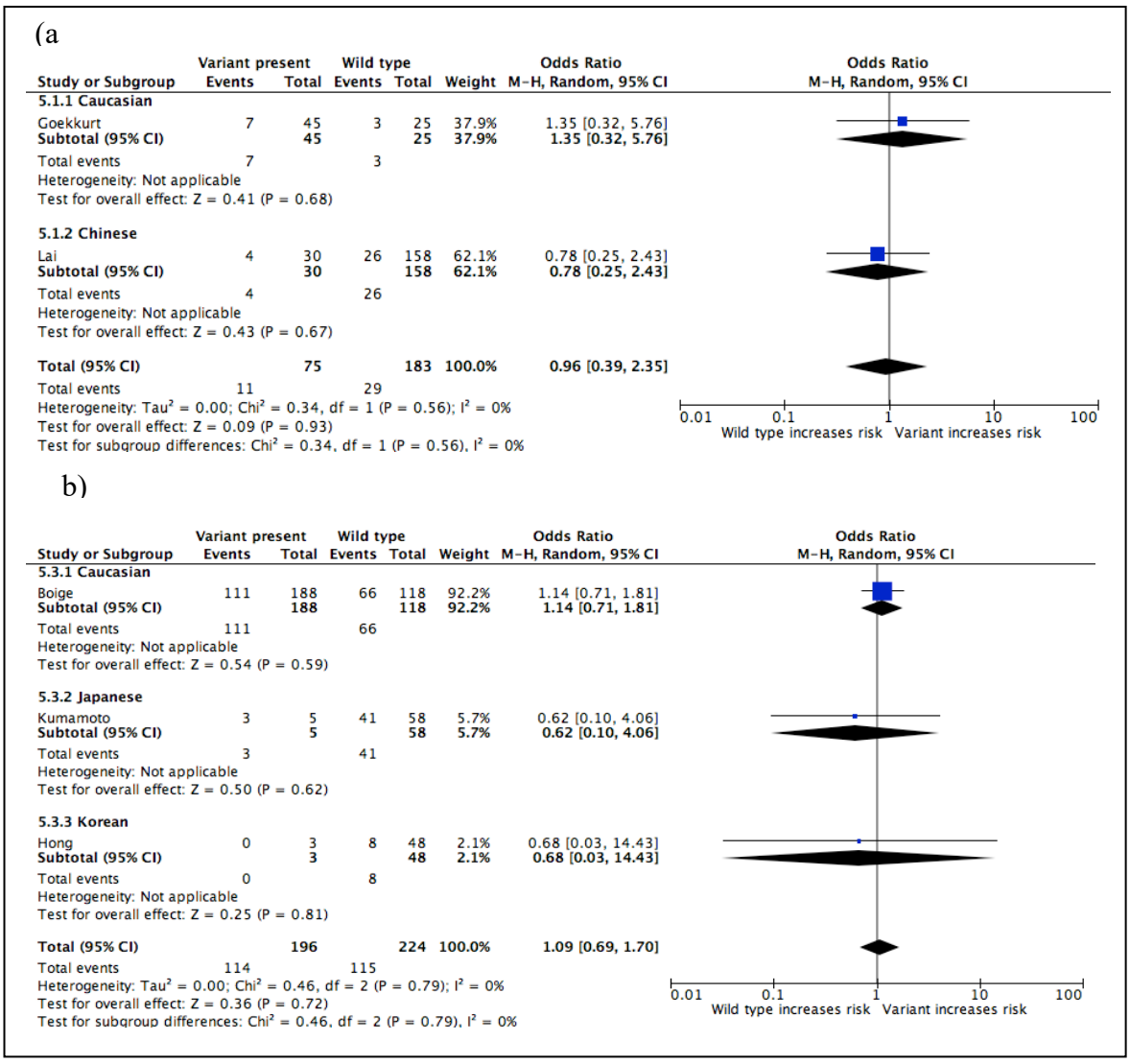


Figure 3.7. Forest plots for association of ERCC2 Lys751Gln and development of (a) NCI CTC grade 3-4 neuropathy and (b) NCI CTC grade 2-4 neuropathy with oxaliplatin

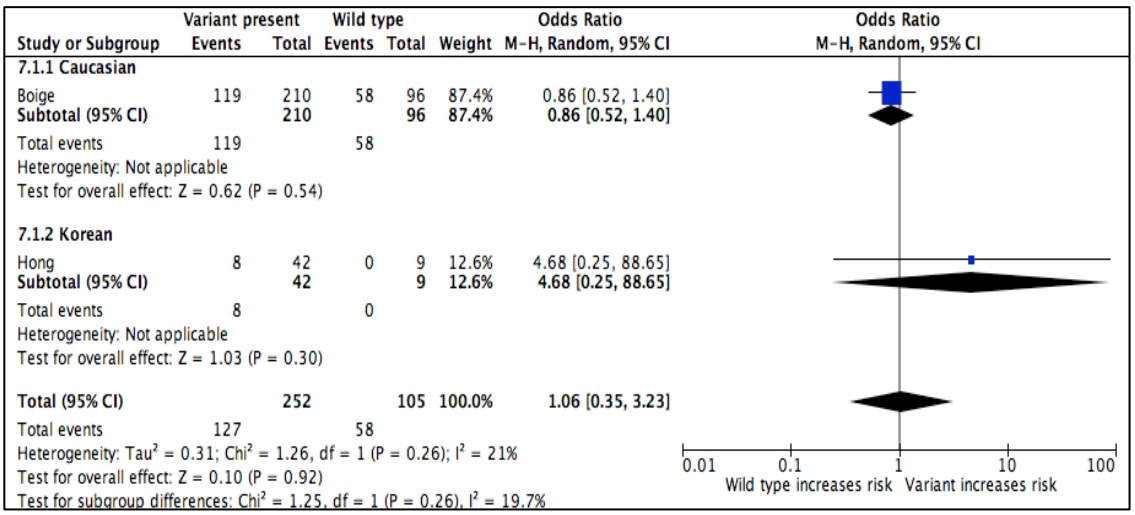


Figure 3.8. Forest plot for association between ERCC2 C156A and development of NCI CTC grade 2-4 neuropathy with oxaliplatin

X ray repair cross-complementing gene 1 (XRCC1)

XRCC1

Platinum

One study reported a protective effect of the GG genotype of *XRCC1 Arg399Gln* against grade 2-4 neuropathy in a Korean population receiving oxaliplatin (348). All further studies demonstrated no effect of this SNP (98, 294, 295, 298-300, 303, 304, 306-308, 312-314, 325, 332, 339, 341, 348) or others including Arg194Trp (295, 304, 307, 308, 341), Arg280His (294, 304, 308, 348), *rs3213239* (304), *rs12611088* and *rs3213255* (294). Five of 13 oxaliplatin-based studies could be included in the meta-analysis for association with *XRCC1 Arg399Gln* (298, 300, 307, 332, 348). This did include the one study which reported a significant association, but overall no evidence of statistically significant association was seen (figure 3.9; OR 0.82, 95% CI 0.38-1.78, I^2=21% and OR 0.98, 95% CI 0.2-4.85, I^2=69%, for NCI CTC grade 3-4 and 2-4, respectively).

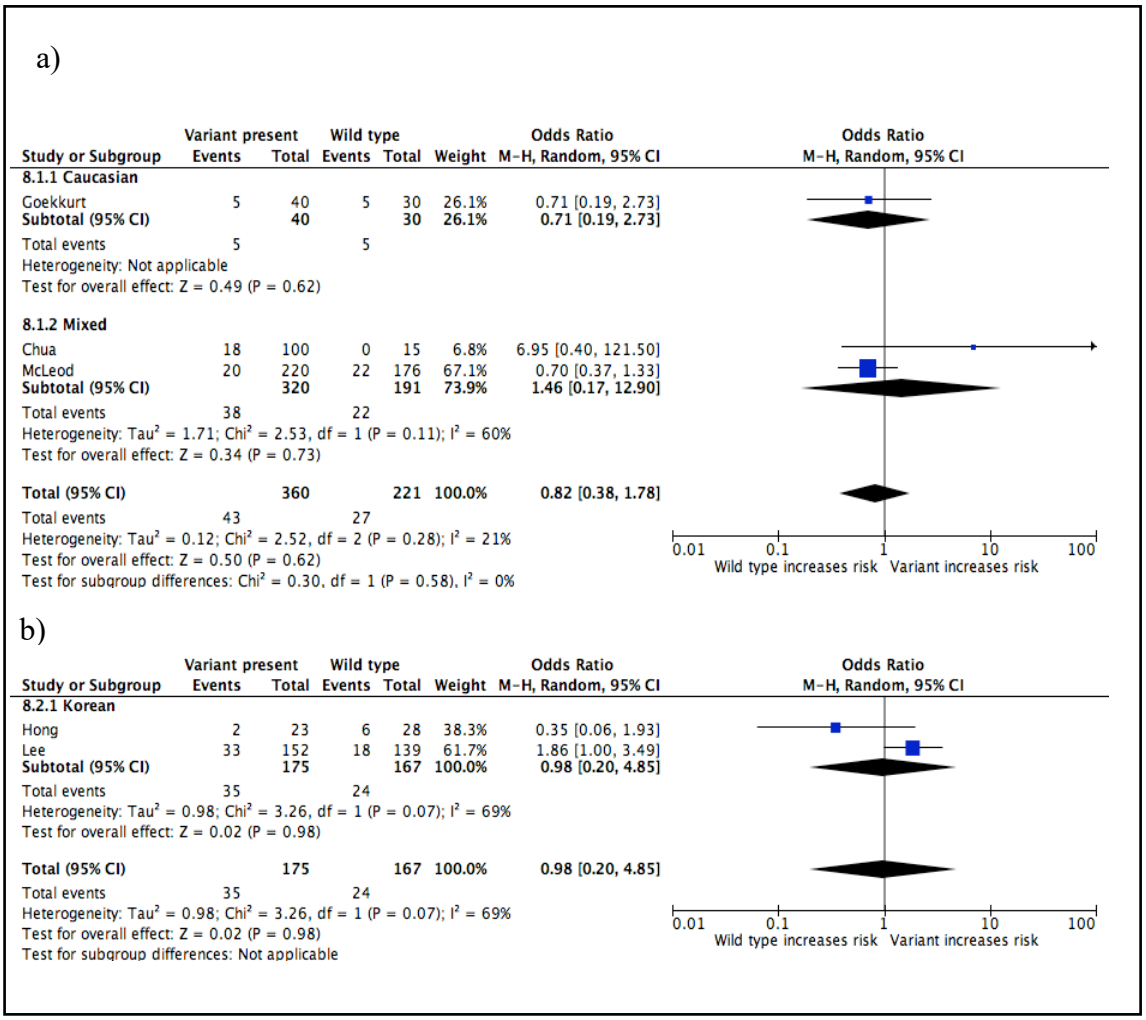


Figure 3.9. Forest plots showing association between XRCC1 Arg399Gln and development of (a) NCI CTC grade 3-4 and (b) NCI CTC grade 2-4 neuropathy with oxaliplatin

Alanine glyosylate aminotransferase gene (AGXT)

AGXT has been investigated by virtue of being involved in the oxalate pathway which is one of the metabolites of oxaliplatin. Five groups of investigators looked for an association with oxaliplatin- induced peripheral neuropathy and the I340M and Pro11Leu SNPs in this gene. One study couldn't perform this analysis due to homogeneity of genotype in their Korean population (348), three showed no effect (302, 304, 307), but one study demonstrated that the minor allele haplotype of these polymorphisms conferred a significantly higher risk of both acute and chronic neurotoxicity of NCI CTC grade 2 or higher in a Caucasian population (90). Three of these studies presented sufficient data for inclusion in a meta- analysis (90, 302, 307), however only two could be entered as the third used a different assessment scale

(302). This showed no significant association (OR 5.23, 95% CI 0.21-129.57, I^2=84%)(figure 3.10).

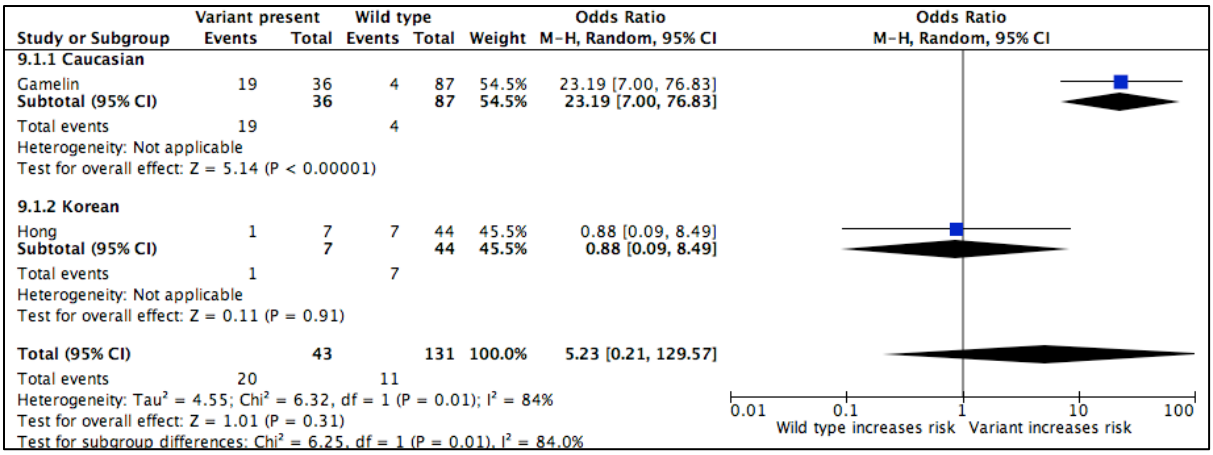


Figure 3.10. Forest plot for association between AGXT I340M and development of NCI CTC grade 2-4 neuropathy with oxaliplatin

X ray repair cross-complementing gene 1 (XRCC1)

ATP- Binding Cassette (ABC) transporters

A summary of the results for this group of genes are reported below but insufficient data was presented in the papers to allow any pooled analysis of results. Only one oxaliplatin (300) and two paclitaxel studies (100, 346) presented their results per neuropathy outcome for each genotype of *ABCB1* SNPs and one of the paclitaxel populations was from the study which used healthy blood donors as controls (346) making this inconsistent with the other study.

ABCB1

ABCB1 and platinum

Five studies demonstrated no effect of the C3435T (294, 300, 304, 314, 339), G2677T/A (294, 300, 314) or C1236T (300, 304, 339) SNPs.

ABCB1 and taxanes/taxane platinum combination

22 studies (82, 100, 103, 274-276, 283, 295, 299, 301, 305, 315, 317, 318, 330, 336, 337, 341-344, 346) investigated an association with *ABCB1* polymorphisms and neuropathy in 21 patient cohorts. Abraham et al (274) found correlations with maximum grade

neuropathy and cumulative dose to sensory neuropathy in three SNPs; *rs2032582* (OR 1.19, 95%CI 1.04-1.36,p=0.02)*, rs1045642* (OR 0.83, 95%CI 0.72-0.95, p=0.009) and *rs3213619* (OR 0.51, 95%CI 0.31-0.85, p=0.004).

Two studies demonstrated a trend for association both in paclitaxel treated patients; One showed a trend for a reduced risk of neuropathy in patients with the CC genotype of the C3453T SNP treated with paclitaxel (275) and another showed a trend towards reduced risk in paclitaxel treated patients who were wild type for the 2677 SNP (305). These and the remaining studies did not find statistically significant associations.

ABCB1 and vincristine

Two studies investigated polymorphisms in this gene in patients treated with vincristine. One studied the C3435T and the G2677T/A polymorphisms (291) but in the other study it was not clear which polymorphisms were investigated (290). Neither study showed any association.

ABCB1 and ixabepilone

This single study investigated C3435T, G2677T/A and C1236T SNPs without any significant association found (310).

ABCC1

ABCC1 and oxaliplatin

Cecchin et al (304) found a significant association between the minor allele at *rs2074087* and development of grade $\geq$2 CIPN (OR= 0.43, 95% CI 0.22-0.86, p=0.017) using an additive model. McLeod (300) and Ruzzo (303) reported no significant association with investigated SNPs (including *rs2074087*).

ABCC1 and taxanes

Seven studies (82, 274, 299, 318, 336, 342, 343) investigated one or more polymorphisms in this gene. None demonstrated an association.

ABCC1 and vincristine

One study was performed in a myeloma population in which >3000 SNPs chosen for potential functional effects were investigated. Permutation testing was carried out to account for the large number of tests. Among the numerous associations found, *rs3887412* in *ABCC1* was found to be associated with an increased risk of grade 2-3 neuropathy after two or three cycles of vincristine (OR 3.36, 95% CI 1.47-7.67, p 5.70 $x10^{-3}$) (293).

ABCC2

ABCC2 and oxaliplatin

Five groups investigated various SNPs in *ABCC2.* Cecchin et al reported a significant association with a number of SNPs in this gene and occurrence $\geq$ grade 2 CIPN (304). Four oxaliplatin studies demonstrated no significant association (90, 300, 303, 348).

ABCC2 and taxanes

Six taxane studies showed no association between SNPs in this gene and neuropathy (82, 299, 318, 336, 343, 344). However, the large Abraham et al study noted associations with two SNPs (*rs8187710* and *rs17222723)* in *ABCC2* from imputed genotype information indicating odds ratios of 0.71 and 0.72 respectively with imputation r^2 =1 (274).

ABCG2

ABCG2 and oxaliplatin

Three studies investigated polymorphisms in *ABCG2*. Custodio et al showed an association between carriers of the AA genotype in *rs3114018* with severe oxaliplatin induced peripheral neuropathy (OR2.67, 95% CI 0.95-4.41, p 0.059) which when combined with their other positive finding (*rs2230641* in *CCNH*), reached statistical

significance (294). Cecchin et al (304) demonstrated an association with *rs2622604,* however this fell below the significance threshold after adjustment for multiple testing. The third study looked at a single different SNP in *ABCG2* and did not show any significant association (300).

ABCG2 and taxanes

Seven studies have been done looking at different SNPs without indication of any association (274, 295, 299, 318, 336, 342, 344). Lamba et al investigated a cohort of patients largely treated with paclitaxel with cisplatin or carboplatin and found a protective effect with the variant allele at *rs13120400* (OR 0.27, 95%CI -2.47- -0.15, p=0.027) (343).

ABCG2 and vincristine

One study showed no association in this population having investigated the *rs2231142* and *rs2231137* polymorphisms (284).

ABCG1

One study that screened 288 Caucasian breast cancer patients treated with paclitaxel for 564 genetic markers (after exclusions) found that *ABCG1* (*rs492338*) crossed the exploratory significance threshold of □=0.001 (homozygous mutant vs homozygote wild-type genotype OR=4.7, 95% CI 1.64-15.57, p=0.002). This was not however replicated in the non- Caucasian patients (296).

Cytochrome P450 gene family

CYP3A4

CYP3A4 and platinum

One oxaliplatin (300) and one high dose carboplatin (333) study investigated and demonstrated no effect of the **1B* or **3* variants.

CYP3A4 and taxanes

No association has been shown with the *1B

(82, 103, 274, 299, 301, 305, 318, 330, 342, 344, 346), *3 (82), *18 (58) *2 (274, 336),*16 variants (274, 344). One large trial of paclitaxel-treated patients of predominantly Caucasian origin showed that in female patients there was a significant association with CYP3A4*22 and development of grade 3 neuropathy in both exploratory and replication cohorts (100). Importantly though there were only two and six patients, respectively, with grade 3 neurotoxicity. A group performing whole exome sequencing of the *CYP3A4* gene in eight patients with grade 3 paclitaxel-induced neuropathy patients identified rare and novel variants, *20, *25 and *27, which along with other CYP3A4 variants, resulted in reduced enzyme expression and were associated with a significantly higher risk of severe neuropathy and a higher probability of requirement of neuropathy-induced treatment modification in a population of 228 patients. They showed a trend towards treatment modification due to CIPN with the *22 variant (345). The only data available that could be combined in meta-analysis was the CYP3A4*22 results from the exploratory and replication cohorts within the DeGraan study (figure 3.11). This showed a statistically significant association with development of NCI CTC grade 2-3 (OR 2.37, 95% CI 1.10-5.12, I^2=0%) and 3-4 (OR 13.98, 95%CI 3.17-61.75, I^2=0%), respectively, although not with any grade neuropathy (OR 1.28, 95% CI 0.68-2.38, I^2=25%).

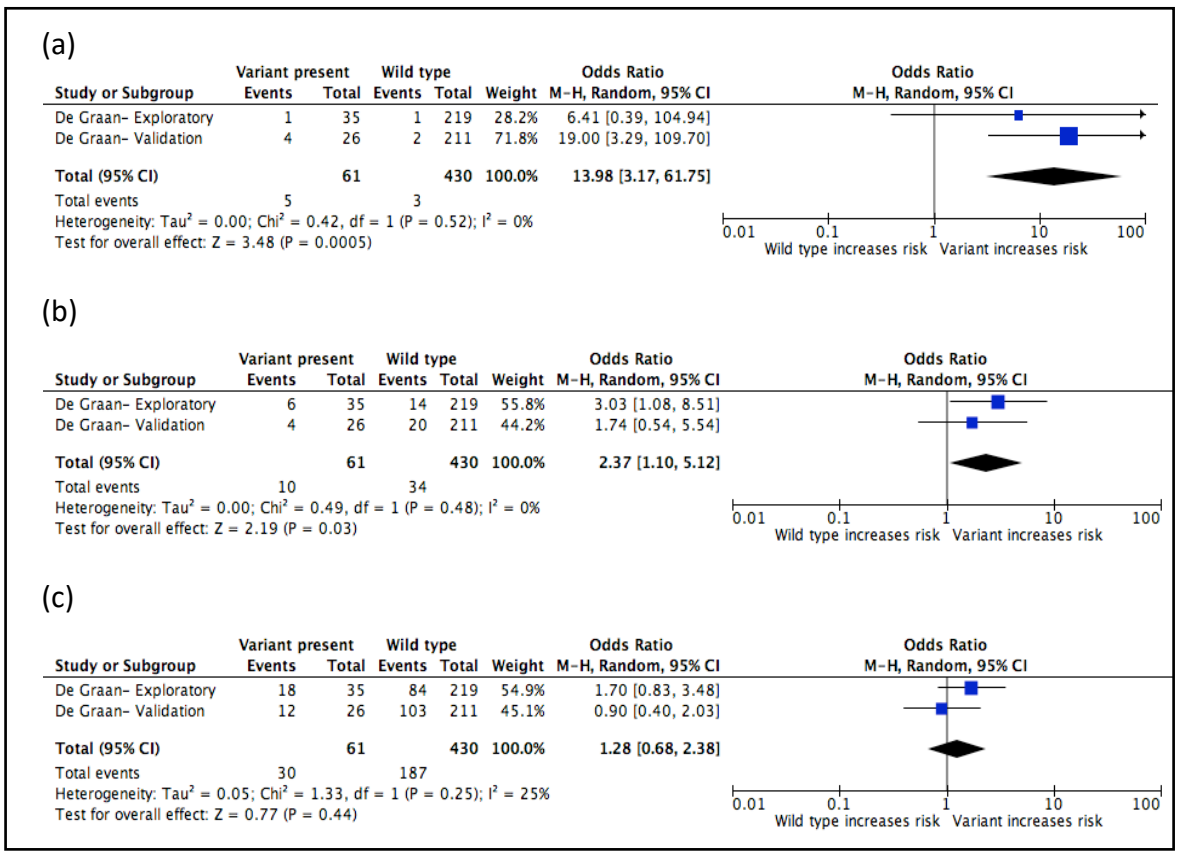


*Figure 3.11. Forest plot for the association of CYP3A4*22 and development of a) NCI CTC grade 3-4, (b) NCI CTC grade 2-4 and (c) any grade neuropathy with paclitaxel*

CYP3A4 and vincristine

Of four vincristine studies, one showed a trend for reduced risk of neuropathy with the *1B allele (41) but none showed any statistically significant association (290-292)

CYP3A4 and ixabepilone

The ixabepilone study (310) showed no effect of the *16 variant.

CYP3A5

CYP3A5 platinum

Again a single oxaliplatin study (300) and a high dose carboplatin study (333) showed no significant association.

CYP3A5 and taxanes

Twelve paclitaxel studies (82, 274, 288, 299, 301, 315, 318, 330, 335, 336, 342, 344) and one docetaxel study (103) were identified. *CYP3A5**3 was the most commonly studied variant. One study showed a significantly reduced risk of neuropathy in 118 patients associated with the *3 variant (per allele HR 0.51, 95%CI 0.3-0.86, p=0.012) (301), while the reminder showed no significant difference.

CYP3A5 and vincristine

Of six studies (41, 71, 73, 290-292), three showed at least a trend for association. In two of the vincristine studies there is likely to be overlap of the paediatric population used as they both genotyped subgroups from the CCG-1891 trial (41, 292). One group showed a significantly reduced risk of neuropathy with the *3 variant allele (291), while a further study showed a trend in this direction (41). One was contradictory and reported the opposite effect (71). *CYP3A5* expressor status was entered into meta-analysis for two eligible studies (figure 3.12). This showed a lack of significant association (OR 0.49, 95% CI 0.19-1.30, I^2=0%) (71, 73).

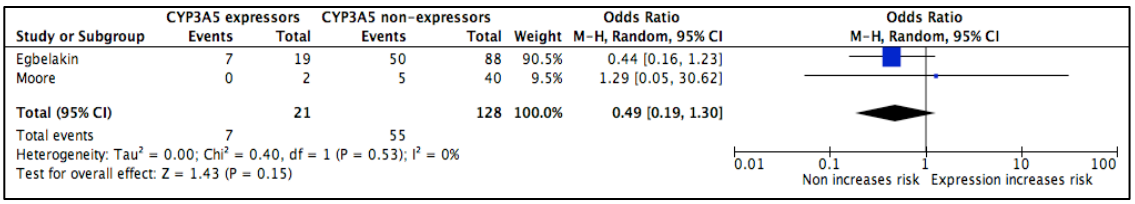


Figure 3.12. Forest plot for association between CYP3A5 expression and development of NCI CTC grade 2-4 neuropathy with vincristine

CYP2C8

CYP2C8 polymorphisms were exclusively investigated in studies focussing on anti-microtubule agents, paclitaxel, docetaxel and ixabepilone. 17 studies were identified, all except one (315) included the *3 allele. The *3 allele was reported as statistically increasing the risk of sensory neuropathy in two studies (HR per allele 1.93, 95% CI 1.05-3.55, p=0.006 and HR per allele 1.72, 95% CI 1.05-2.82, p=0.032, respectively)

(281, 301). A third study by Hertz et al using at least some of the same population showed that patients with a 'low metaboliser CYP2C8 phenotype' (those with *2,*3 or *4 variants) were at increased risk of neuropathy, although *2 and *4 SNPs were not independently associated (296). In addition a further study has shown increasing motor neuropathy with the *3 SNP (OR not stated) (305) and a fifth has reported a trend in this direction (330). Only two studies presented sufficient data for inclusion in meta-analysis of this association (figure 2.13) (100, 330). Leskela et al also demonstrated a reduced risk of neuropathy with the HapC allele (301). The remainder of the studies reported no significant effects in investigated SNPs (82, 100, 299, 310, 315, 318, 335-337, 343, 344, 346).

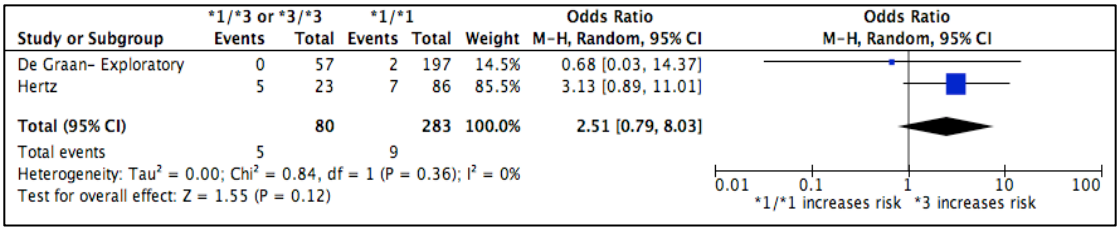


*Figure 3.13. Forest plot for the association of CYP2C8*3 and development of NCI CTC grade 3-4 neuropathy with paclitaxel*

Table 3.9. Details of studies included in meta-analyses and reasons for exclusions

Variant	Drug	Number of studies	Meta-analysis performed Y/N	Outcomes	Studies included	Studies excluded and reason
GSTP1 Ile105Val	Oxaliplatin	27	Y	Any grade CIPN NCI CTC grade 2-4 NCI CTC grade 3-4 Oxaliplatin-specific scale grade 2-4 Oxaliplatin-specific scale grade 3-4	2 studies (279, 320) 5 studies (90, 94, 297, 307, 319) 6 studies (279, 298, 300, 309, 311, 327) 3 studies (302, 316, 320) 4 studies (302, 306, 320, 352)	11 were excluded due to insufficient results presented (215, 273, 294, 303, 304, 312-314, 325, 339, 348)
	Cisplatin	4	N	NA	No eligible studies	Insufficient definition of outcome (98) Inconsistent outcome measure (338, 347) Insufficient data presented (308)
	Taxanes	9	N	NA	Only 1 study presented numbers of patients per genotype (329)	Insufficient data presented (82, 103, 295, 299, 341, 342, 344)
	Vincristine	3	N	NA	Only 1 study presented numbers of patients per genotype(324)	Insufficient data presented (291, 292)
GSTP1 Ala114Val	Oxaliplatin	5	N	NA	No eligible studies	Different assessment scales used and different outcomes studied (90, 95, 297) Insufficient data reported (294, 304)
	Cisplatin	1	N	NA	No eligible studies	Single study, insufficient data reported (308)
	Taxanes	6	N	NA	No eligible studies	Insufficient data reported (103, 274, 295, 299, 329, 342)
GSTM1 deletion	Oxaliplatin	11	Y	NCI CTC Grade 2-4 NCI CTC Grade 3-4	2 studies (297, 319) 3 studies (298, 300, 309)	Data reported but different assessment scale used (95) Insufficient data reported (304, 306, 312, 348) Insufficient data plus mixed with cisplatin (215)
	Cisplatin	4	N	NA	Only one study reported data per genotype (298)	Insufficient data (98, 308, 338) and regimens with differing neurotoxic potential (98, 338)
	Taxanes	2	N	NA	Only one (docetaxel) study reported data per genotype (329)	Insufficient data presented (paclitaxel) (341)
	Vincristine	3	N	NA	Only 1 study presented numbers of patients per genotype (324)	Insufficient data presented (291, 292)
GSTT1 deletion	Oxaliplatin	9	Y	NCI CTC grade 2-4 NCI CTC grade 3-4	2 studies (297, 319) 2 studies (298, 309)	Data presented but different assessment scale used (95).

						Insufficient data presented (306, 312, 339, 348)
	Cisplatin	3	N	NA	Only one study reported data per genotype (298)	Insufficient data (308, 338) and regimens with differing neurotoxic potential (338)
	Taxane	2	N	NA	Only one (docetaxel) study reported data per genotype (329)	Insufficient data presented (paclitaxel) (341)
	Vincristine	3	N	NA	Only 1 study presented numbers of patients per genotype (324)	Insufficient data presented (291, 292)
ERCC1 C118T	Oxaliplatin	20	Y	NCI CTC grade 3-4 NCI CTC grade 2-4	4 studies (298, 300, 309, 332) 4 studies (94, 297, 307, 319)	Insufficient data presented (294, 303, 304, 306, 311-314, 325, 327, 339, 348)
	Cisplatin	3	N	NA	Only one study presented numbers of patients per genotype (298)	Insufficient data presented (98, 308)
	Taxanes (with carboplatin)	3	N	NA	No eligible studies	Insufficient data presented (295, 299, 341)
ERCC1 C8092A	Oxaliplatin	8	Y	NCI CTC grade 3-4 NCI CTC grade 2-4	2 studies (298, 309) 2 studies (94, 307)	Insufficient data presented (304, 311, 313, 348)
	Cisplatin	2	N	NA	Only one study presented numbers of patients per genotype (298)	Insufficient data presented (308)
	Taxanes (with carboplatin)	3	N	NA	No eligible studies	Insufficient data presented (295, 299, 341)
ERCC2 Lys751Gln	Oxaliplatin	16	Y	NCI CTC grade 3-4 NCI CTC grade 2-4	2 studies (298, 331) 3 studies (297, 307, 319)	Insufficient data presented (294, 300, 303, 304, 306, 311-313, 325, 327, 348)
	Cisplatin	3	N	NA	Only one study presented numbers of patients per genotype (298)	Insufficient data presented (98, 308)
	Taxanes (with carboplatin)	3	N	NA	No eligible studies	Insufficient data presented (295, 299, 341)
ERCC2 Asp312Asn	Oxaliplatin	10		NCI CTC grade 3-4	Only one study presented numbers of patients per genotype (298) 2 studies(297, 307)	Insufficient data presented (294, 303, 304, 306, 311, 313, 348)
	Cisplatin	3	N	NA	Only one study presented numbers of patients per genotype(298)	Insufficient data presented (98, 308)
ERCC2 C156A	Oxaliplatin	4	Y	NCI CTC grade 2-4	2 studies (297, 307)	Insufficient data presented (313, 348)
XRCC1 Arg399Gln	Oxaliplatin	14	Y	NCI CTC grade 3-4 NCI CTC grade 2-4	3 studies (298, 300, 332)	Insufficient data presented (294, 303, 304,

					2 studies (307, 348)	306, 312-314, 325, 332, 339)
	Cisplatin	3	N	NA	Only one study presented numbers of patients per genotype (298)	Insufficient data presented (98, 308)
	Taxanes (with carboplatin)	3	N	NA	No eligible studies	Insufficient data presented (295, 299, 341)
XRCC1 Arg194Trp	Oxaliplatin	2	N	NA	Only one study presented numbers of patients per genotype (307)	Insufficient data presented (304)
	Taxanes (with carboplatin)	2	N	NA	No eligible studies	Insufficient data presented (295, 341)
XRCC1 Arg280His	Oxaliplatin	4	N	NA	Only one study presented numbers of patients per genotype (307)	Insufficient data presented (294, 304, 348)
AGXT I340M	Oxaliplatin	5	Y	NCI CTC grade 2-4	2 studies (90, 307)	Data presented but different assessment scale (302) Insufficient data presented (304, 348)
AGXT Pro11Leu	Oxaliplatin	4	N	NA	Only one study presented numbers of patients per genotype (90)	Insufficient data presented (302, 304, 348)
ABCB1 C3435T	Oxaliplatin	5	N	NA	Only one study reported numbers of patients per genotype (300)	Insufficient data presented (294, 304, 314, 339)
	Taxanes	21	N	NA	Only one study remaining after exclusions (100)	Insufficient data presented (82, 103, 274-276, 283, 299, 301, 305, 315, 318, 330, 336, 337, 341-344) Inconsistent control group used (346). Two highly neurotoxic agents used concurrently (317)
ABCB1 G2677T/A	Oxaliplatin	3	N	NA	Only one study reported numbers of patients per genotype (300)	Insufficient data presented (314, 339)
	Taxanes	17	N	NA	No eligible studies	Insufficient data presented (82, 103, 274-276, 283, 299, 301, 305, 315, 318, 336, 337, 341, 343, 344). Inconsistent control group used (346)
ABCB1 C1236T	Oxaliplatin	3	N	NA	Only one study reported numbers of patients per genotype (300)	Insufficient data presented (304, 339)
	Taxanes	16	N	NA	No eligible studies	Insufficient data presented (82, 103, 200,

						274-276, 299, 301, 305, 318, 336, 337, 342-344)
*CYP3A4*1B*	Taxanes	11	N	NA	No eligible studies	Insufficient data presented (82, 103, 274, 299, 301, 305, 318, 330, 342, 344, 346)
	Vincristine	2	N	NA	One study reported numbers of patients with neurotoxicity per genotype (41)	Insufficient data presented (291)
*CYP3A4*2*	Taxanes	2	N	NA	No eligible studies	Insufficient data presented (274, 336)
*CYP3A4*16*	Taxanes	2	N	NA	No eligible studies	Insufficient data presented (274, 344)
*CYP3A4*22*	Taxanes	1	Y	NCI CTC grade 3-4 neuropathy, grade 2-4 neuropathy and any grade neuropathy	Exploratory and replication cohorts within one study (100)	
*CYP3A5*3*	Taxanes	8	N	NA	Only one study presents numbers of patients per genotype (288)	Insufficient data presented (82, 103, 200, 301, 318, 335, 336, 342)
	Vincristine	4	Y	NCI CTC grade 3-4	2 studies (71, 73)	Insufficient data presented (41, 291)
*CYP3A5*3C*	Taxanes	2	N	NA	No eligible studies	Insufficient data presented (299, 330)
*CYP3A5*6*	Vincristine	3	N	NA	No eligible studies	Insufficient data presented (73). Data presented but different outcomes and classification used (41, 71)
*CYP2C8*3*	Taxanes	16	Y	NCI CTC grade 3-4	2 studies (100, 330)	Insufficient data presented (82, 274, 281, 296, 299, 301, 305, 318, 335-337, 343, 344, 346)
*CYP2C8**4	Taxanes	8	N	NA	Only one study presented data per genotype (100)	Insufficient data presented (82, 274, 296, 299, 301, 337, 344)
*CYP2C8**1B	Taxanes	4	N	NA	No eligible studies	Insufficient data presented (82, 274, 301, 344)
*CYP2C8**2	Taxanes	5	N	NA	No eligible studies	Insufficient data presented (82, 274, 305, 337, 344)
*CYP2C8 *HapC*	Taxanes	5	N	NA	No eligible studies	Insufficient data presented (82, 274, 301, 335, 344)

3.3.4 Significant associations in other less commonly investigated variants

Platinum studies

Antonacopoulou et al showed an increased severity of chronic oxaliplatin- induced peripheral neuropathy with the TT genotype at residue 33 of the *ITGB3* gene in 55 FOLFOX-4 treated patients in a single candidate SNP study (p= 0.044) (277). Argyriou et al investigated a link between the *SCNA* genes (coding for voltage- gated sodium channel proteins) and showed an association between *SCN4A rs2302237* (OR 2.47, 95%CI 1.04-5.85, p= 0.037) and increased risk of chronic oxaliplatin of any grade in a cohort of 200 patients treated with either FOLFOX or XELOX. Four SNPs were investigated without adjustment for multiple testing and analysis was undertaken using dominant, recessive and overdominant models. The overdominant (and presumably most positive) model is presented (88).

Basso et al investigated oxaliplatin related acute neurotoxicity specifically after one cycle of treatment, and a possible genetic link with nerve hyperexcitability through variation in a calcium-dependent potassium channel abundantly present in the peripheral nervous system encoded by the *SK3* gene. They reported that of their relatively small population, those with the 13-14 CAG repeat allele may be more susceptible to the acute neurotoxicity seen with oxaliplatin, whilst those with >15 repeats may be protected (OR with >15 repeats; 0.381, 95%CI 0.247-0.590, p=0.001) (280).

Johnson et al (217) genotyped a cohort of 400 lung cancer patients treated with a platinum agent. Some of these patients received a taxane. The heterogeneity of the treatment received is a limitation but whether or not patients received a concurrent taxane was accounted for in a multivariate analysis. *Rs3753752* in the *GPX7* gene was found to have a significant association with development of CIPN after adjustment and correction for multiple testing with the variant allele associated with an OR 1.7 (95%CI 1.20-2.40, p=0.0028).

Taxane studies

A large study analysing SNPs in the Fanconi anaemia/ BRCA pathway in 888 breast cancer patients receiving either weekly or bi-weekly paclitaxel demonstrated association of four SNPs in the FANCD2 gene with development of grade 3-4 neurotoxicity *rs7648104*; OR 1.86, 95%CI 1.3-2.65; *rs7637888*; OR 1.87, 95% CI 1.30-2.67*; rs6786638*; OR 1.90, 95% CI 1.32-2.72; *rs6442150*; OR 1.89, 95% CI 1.32-2.72) (328). Imputed results for these SNPs from a GWAS failed to confirm an association (HR 0.93, 95% CI 0.77-1.13, p=0.46 for all four SNPs) (274).

A study of ovarian cancer patients from a phase III trial population treated with either paclitaxel or docetaxel with carboplatin investigated 1261 SNPs within 60 genes (295). They divided their cohort into a discovery and a replication set, and both groups contained docetaxel- and paclitaxel- treated patients. Correction for multiple testing was performed. 69 SNPs were associated with development of grade 2 or greater CIPN in the discovery set, of which four of these associations were confirmed in the replication set. These four SNPs were *rs139887* (*SOX10*) (OR 1.77 95% CI 1.21-2.59, p=0.001), *rs2849380* (*BCL2*) (OR 2.82 95%CI 1.16-6.88, p=0.013), *rs544093* (*OPRM1*) (OR 1.67 95%CI 1.017- 2.73, p=0.015) and *rs879207* (*TRPV1*) (OR 1.62 95%CI 1.11- 2.37, p=0.002). OPRM1 has been associated with sensitivity to pain (353).

SNPs involved in the variability of beta- tubulin expression were retrospectively investigated in 214 paclitaxel-treated patients. A large variation in the expression of beta-tubulin IIa was demonstrated with variants in the *TUBB2A* gene (-101 and -112) whilst increasing transcription of the protein product conferred protection from CIPN (HR 0.62 95% CI 0.42-0.93, p=0.021) (285). Imputed genotype data from the Abraham study demonstrated an association with the *TUBB2A rs9501929* SNP (HR 1.6 95%CI 1.18-2.18) (274). In contradiction to these results, Eckhoff et al found no association with four SNPs in the *TUBB2A* gene, including *rs9501929* (HR not stated) and CIPN in a case-control study of 150 docetaxel treated breast cancer patients (103).

Lee et al (315) investigated candidate SNPs selected for having a role in either paclitaxel or gemcitabine metabolism or action in a cohort of 85 patients receiving both drugs. They demonstrated an increased risk of CIPN for those with the AA genotype for *rs9937* in *RRM1* although this was not repeated on multivariate analysis. Of note *RRM1* was

selected for a role in gemcitabine action rather than being thought to affect paclitaxel effect.

Beutler et al investigated for association of development of paclitaxel- induced peripheral neuropathy with SNPs in genes known to be implicated in Charcot-Marie-Tooth (CMT) disease. They included patients from an observational study investigating the occurrence of CIPN with either weekly or three-weekly paclitaxel. 73 cases and 46 controls were identified using rate of change of EORTC CIPN20 scores throughout treatment. Two genes were found to be implicated in development of CIPN; variants in *PRX* and three non-synonymous SNPs in *ARHGEF10* (321). The same group replicated the association of three ARHGEF10 SNPs using similar methodology in a separate prospectively recruited cohort. They confirmed the increased risk of CIPN associated with *ARGHGEF10* variants, in particular *rs9657362* (OR 3.56, p=0.018) (322).

Vincristine studies

In vincristine induced peripheral neuropathy, Kishi et al noted a significant association with *VDR* intron 8 AA genotype and increased risk of peripheral neuropathy (OR2.16, 95% CI 1.03-4.51, p=0.042 (291) and Sepe et al reported a positive association with *TSbp* 28 insertion (292).

3.3.5 Genome wide association studies

Oxaliplatin

Five genome- wide association studies are included in this review. The Abraham study is part of a genome-wide association study but only replication data of putative SNPs have been published so far. Two further genome- wide association studies were identified but only the abstracts are available for these and are mentioned but not included in the full systematic review (271, 354).

The first genome wide study performed involved 96 and 247 Korean patients in discovery and replication sets, respectively. They were treated with oxaliplatin and association was sought for those who experienced > grade 2 neuropathy or those

experiencing grade 2 chronic neuropathy for > 7 days. They identified nine significant SNPs, the most significant association that they observed was in *TAC1* (*rs10486003*) (OR 0.32, 95%CI 0.19-0.52, p=4.84x10^{-7}). The *TAC1* gene encodes four members of the tachykinin family, including substance P, which are thought to act as neurotransmitters [Gene, 2017 #4112] . Four other SNPS were found to be significant in a multiple regression analysis (*rs2338* (OR2.27, 95%CI 1.58-3.26,p=4.63x10^{-6})*, rs830884* (OR 0.32, 95%CI 0.19-0.54*,* p=1.74x10^{-6}), *rs843748* (OR2.43, 95%CI 1.61-3.68,p=1.01x10^{-5}) and *rs797519* (OR0.50, 95%CI 0.35-0.72, p=8.21x10^{-5}) (272). A retrospective study in a Japanese population of 70 colorectal cancer patients treated with modified FOLFOX6 attempted to validate the top nine hits from the Korean GWAS (94). They used the same criteria for defining a 'case' of neuropathy. The study is clearly limited by its retrospective nature but measures were put in place to aim for consistency in assessing the phenotype of patients. In univariate analysis, they found that two of the SNPs were significantly related to developing neuropathy, *rs843748* in *ACYP2* (p=0.056) and *rs17140129* in *FARS2* (p=0.072). The *FARS2* SNP remained significant in multiple logistic regression analysis (OR 6.5, 95%CI 1.2-35.7, p=0.034). Additionally, *rs10486003* in *TAC1* was associated with time to onset of chronic neuropathy. A replication study in an Italian population demonstrated only a trend towards a protective effect of the *FARS2* SNPs (OR 0.34, 95%CI 0.09-1.22, p=0.081 for *rs17140129*) and of *rs843748* in *ACYP2* when using the TNSc (OR 0.27, 95%CI 0.10-0.75,p=0.008; significance lost on multi-test adjustment) (89).

A second GWAS study looking at colorectal cancer patients aimed to examine associations with a range of 5-Fluorouracil or FOLFOX toxicities. With regard to investigating an association with oxaliplatin- induced peripheral neuropathy, there were 133 patients in a discovery set and 324 patients in a replication cohort. The strongest associated SNPs only reached significance at the <10^{-4} level, so none reached the generally accepted level for genome wide significance. These hits were not found to be significant when examined in the replication cohort (273).

Taxanes

A GWAS in a Caucasian paclitaxel-treated population of 855 breast cancer patients identified a SNP (*rs10771973*) in the *FGD4* gene (HR 1.57, 95%CI 1.30-1.91, $p=2.6x10^{-6}$) (82). This was replicated in both Caucasian and African American replication cohorts. A second SNP, in *EPHA5*, a gene with biological plausibility, showed significant association in the discovery set only (HR1.63, 95% CI 1.34-1.98, $p=9.6x10^{-7}$).

A further GWAS in a population of 144 Caucasian patients treated with paclitaxel and carboplatin for a variety of primary cancers found an association with *rs17348202* in close proximity to the *EPHA4* gene (HR 4.85, 95% CI 2.57-9.13, $p=1.02x10^{-6}$) with other top hits including *rs4141404* and *rs2413045* in the *LIMK2* gene (HR2.41, 95% CI 1.66-3.48, $p=3.22x10^{-6}$; HR 2.36, 95%CI1.57-3.56, $p=3.67x10^{-5}$, respectively) and *rs3829306* in *SLCO1B1* (HR3.10, 95% CI 1.82-5.26, $p=2.84x10^{-5}$). This group performed meta-analysis of the two paclitaxel-based GWAS within which two SNPs crossed the genome-wide significance level; *rs7349683* in *EPHA5* (HR=1.68, 95% CI 1.42-1.99, $p=1.4x10^{-9}$) and , *rs4737264* in *XKR4* (HR=1.71, 95% CI 1.41-2.06,$p=3.11x10^{-8}$) (85).

An abstract based on interim analysis of a GWAS presented at the American Society of Clinical Oncology (ASCO) meeting 2011 reported the most significant findings in relationship to neuropathy were SNPs in *RWDD3 rs2296308* (HR per allele 1.5, $p=8.5x10^{-8}$) and *TECTA rs1829* (HR2.07, $p=3.15x10^{-7}$) (354) There does not appear to be a full publication of this work to date. Attempted replication of association with these SNPs have either shown no association or contradictory results (323, 334).

A further GWAS presented thus far in abstract form only was that by Hertz et al at ASCO 2013 (271). It reported results of a GWAS in docetaxel- treated castrate- resistant prostate cancer patients treated within a large phase III clinical trial. They report their top hit *rs11017056,* which met the significance level for genome wide significance. However, neither this SNP, nor several others selected were replicated in a cohort of paclitaxel treated breast cancer patients.

Vincristine

A GWAS in a paediatric acute lymphoblastic leukaemia population involved 321 and 222 children respectively in two prospective US-based clinical trial cohorts. All children were treated for acute lymphoblastic leukaemia with chemotherapy regimens involving 36-39 doses of vincristine. The investigators identified a SNP in the promoter region of *CEP72 (rs924607*) which was associated with development of grade 2-4 vincristine-related neuropathy with 56% of patients with the homozygous variant genotype developing this complication compared with 21.4% of those with the heterozygote or wild type genotype ($p=6.3x10^{-9}$) (72). A replication study in a Spanish paediatric ALL trial cohort involving 142 patients however did not confirm this association (OR 0.65, 95% CI 0.17-2.43, p=0.5), albeit they focussed on neurotoxicity developing during the induction phase of chemotherapy only (289).

3.4 DISCUSSION

There have been concerns raised in the literature regarding the methodological quality of pharmacogenetics studies (267, 355). This can greatly affect reproducibility of results and lead to false conclusions being drawn. This in turns leads to difficulty in interpretation and ability to apply results to clinical practice. This review identifies many methodological issues with the current literature regarding the pharmacogenetics of CIPN.

Study size was generally small. Based on previous evidence regarding sample size needed to ensure sufficient power in pharmacogenetics studies, most studies were likely underpowered to detect a statistically significant relationship with a genetic variant (267). Power calculations were rarely undertaken and in the majority of studies the reader was uninformed of the likelihood of detecting a significant genetic effect, if indeed one exists.

Many studies lacked sufficient detail upfront as to how analysis was undertaken and endpoints investigated leading to the risk of within-study selective reporting. In many

studies, the outcomes in terms of peripheral neuropathy were not pre-stated and the mode of inheritance assumed for analysis is not disclosed; we therefore do not know if several modes of inheritance and outcomes had been analysed with only the most significant being presented, thus inflating the type I error rate.

For many of the studies CIPN is one of many survival, response and toxicity outcomes examined. Partly as a consequence there is frequently lack of detail in phenotype definition, which is fundamental to the accuracy of results. CIPN is a challenging adverse reaction to study due to its subjective nature and the fact that there is a lack of an ideal assessment tool or measure. Particular care is therefore needed in definition of 'cases' and 'controls'. Some studies however appear to fail to make fundamental considerations. In the case of oxaliplatin, many studies did not differentiate between acute and chronic neurotoxicity. Given the different mechanisms of the two forms, it is unlikely that grouping these together will yield consistent phenotypic categories and therefore genotyping results may be meaningless. Many studies did not exclude patients with pre-existing neuropathy and most failed to consider that there may be relevant clinical covariates such as diabetes, alcohol excess or differential neurotoxic potential of the various drug regimens used in their study cohort. There is a balance to be struck between including different regimens of the same drug in study cohorts in order to allow larger populations to be studied and keeping the clinical characteristics as uniform as possible.

A more significant problem existed in a handful of studies, however, where patients were treated with differentially neurotoxic chemotherapy regimens including for example carboplatin and cisplatin in the same cohort and cohorts where some patients were receiving a second potentially neurotoxic agent in addition to the index drug. The fact that many studies do not state minimum dose criteria to be received by patients classed as 'control' subjects raises the question as to whether they are true control subjects if they received only a small dose of the neurotoxic agent if it was stopped early for other toxicity such as hypersensitivity or myelosuppression. Many studies were prospective and had clear plans for assessment of CIPN; however a significant number relied upon case-note review for assessment as to the degree of neurotoxicity. It has been well documented that physicians frequently underestimate the severity of

this side effect (140, 356, 357) and therefore there are major inaccuracies in relying on documented information alone for assessing presence/ absence and severity of CIPN. It was disappointing how few studies presented their results to allow meta-analysis. This limits the usefulness of the meta-analyses performed along with the heterogeneous nature of many of the studies.

A solution could be formation of a consortium for investigating pharmacogenetics of chemotherapy related toxicity which would allow investigators to share individual data and undertake individual patient data meta-analysis. Formation of such expert working parties would also allow standardisation of phenotype definition which has been an invaluable process in other fields (358, 359). Increasingly cumulative dose to NCI CTC grade 2 neuropathy has been used as an outcome. There are pitfalls with this due to inconsistencies in rating between grade 1-2 neuropathy (140) and in accurately differentiating a case from a control patient, in particular for oxaliplatin-induced neuropathy where the phenomenon of coasting is common (when a patient completes all planned chemotherapy only to develop grade 3 neurotoxicity very shortly afterwards) and this phenotypic information is lost in this outcome measure. A solution could be a combination of a standard scale such as NCI CTC or TNSc and a patient report outcome, or a more descriptive explanation of the terms used in the grade definitions to ensure high inter-rater consistency.

There are a small number of interesting SNPs emerging as potential factors in this complex, seemingly polygenic susceptibility to CIPN which require well-planned, methodologically robust studies to attempt to validate them. As well as complying with published guidelines of standards for pharmacogenetics studies, extreme care is needed to fully define and meticulously categorise patient phenotype prior to undertaking genotypic analysis. Those SNPs particularly warranting further investigation in association with taxane-induced neuropathy would appear to include; CYP2C8*3 due to positive associations seen in a number of studies (281, 301, 305); CYP3A4*22 due to its positivity in one large trial in both discovery and replication sets (100) and lack of any independent replication to date; TUBB2A SNPs as identified by one candidate gene approach (285) and confirmed of interest in a large replication study (274) albeit not confirmed in a docetaxel cohort (103); the EPHA genes, given data available from two published GWAS (82, 85); and the CMT-associated genes investigated by Beutler and

Boora et al (321, 322); ABCC2 SNPs also warrant further investigation. For oxaliplatin-induced neuropathy, the list is shorter. The three most statistically significant SNPs in the Japanese GWAS (272) partially replicated in a second Japanese population (94) could be investigated further, albeit one study in a Caucasian population has only shown one weakly positive outcome with one of the group of SNPs (89). Finally, for vincristine neuropathy CEP75 variants (72) and CYP3A5*3 may warrant further investigation (41, 71, 291). Whole exome sequencing may also lead to further rare variants in genes affecting drug metabolism which may prove to be significant. It is evident so far that any genetic variant which could confer susceptibility to CIPN is likely to have a relatively small effect size and that rather than finding one or two high risk SNPS, that eventually a panel of susceptibility variants may be identified and combined in a polygenic risk score.

3.5 CONCLUSION

Much work is needed in this area to investigate pharmacogenetic associations to aim towards better risk stratification of potential chronic neuropathy which may affect return to normal function after a course of chemotherapy. Improving quality of methodology, in particular, in phenotypic definition and clinical assessment is however essential to aim towards more meaningful, clinically applicable findings.

CHAPTER 4

PHARMACOGENETIC STUDY: A CANDIDATE GENE STUDY TO INVESTIGATE PUTATIVE ASSOCIATIONS WITH CIPN

4.1 INTRODUCTION

There is a clear need for further pharmacogenetic studies in the investigation of chemotherapy induced peripheral neuropathy (CIPN) to further our knowledge of this complex adverse effect. The systematic review presented in chapter 2 highlighted the methodological flaws and areas for focus based on comprehensive review of previous work in this area. It is important to note that the systematic review presented in chapter 2, whilst updated in 2016 to ensure completeness for publication and thesis submission, was initially evaluated 18 months prior to the final search to allow progress with our clinical study and decision on the array of SNPs for review in our investigation.

4.1.1 Taxane study

In the field of taxane-induced peripheral neuropathy, seven putative variants were selected based on suggestive candidate gene or genome-wide association studies; *CYP3A4*22, CYP2C8*3, FGD4 rs10771973, EPHA4 rs17348202, EPHA5 rs7349683, EPHA6 rs301927, XKR4 rs4737264.*
It has been shown that paclitaxel pharmacokinetics with exposure to higher drug levels during the cycle is associated with an increased risk of neuropathy (29, 360, 361), and so it follows that variants in genes coding for enzymes involved in the metabolic pathways of taxanes have been studied. This has largely been without demonstration of any association with neurotoxicity. However, of these variants, a selected few do look of interest.

*CYP3A4*22* had been studied in a relatively large cohort of patients who had received paclitaxel for a variety of solid tumours (361). The variant allele is known to lead to lower CYP3A4 activity of which the taxanes are known substrates. In female patients, this SNP was shown to be significantly associated with development of NCI CTC grade 3 neuropathy in both exploratory and replication cohorts (122 and 110 patients, respectively). Exploratory analysis combining the two cohorts revealed an increased risk of grade 3 neurotoxicity in *CYP3A4*22* variant carriers (HR=22.1 95%CI 4.7-105,

p<0.001). Only a small number of cases were included in this cohort and so these results must be treated with caution; however the biological plausibility of this finding warrants further investigation.

*CYP2C8*3* had been studied in fifteen TIPN studies (29, 82, 274, 281, 296, 299, 301, 318, 330, 336, 337, 343, 344, 361, 362), although three of these included overlapping patient cohorts (281, 296, 330). Four of the studies reported a significant association with the development of TIPN (29, 281, 296, 301) and a fifth reported a trend in this direction (330).

Of the SNPs related to taxane metabolic pathways, we elected to attempt replication of the association with *CYP3A4*22* and *CYP2C8*3* in our patient cohort.

Table 4.1 Summary of evidence to support SNP selection for candidate gene study

Gene and SNP	Study	Findings to date	Effect estimate (95%CI, p value)	Biological relevance
*CYP3A4*22*	Apellaniz-Ruiz 2015 (345)*	Trend towards need for treatment modification	Not stated (p=0.066)	The variant allele is known to be related to lower CYP3A4 activity of which the taxanes are known substrates
	DeGraan 2013 (361)	Significant association with development of NCI CTC grade 3-4 CIPN	OR 19.1 (3.3-110, p=0.001) in validation cohort	
	Meta-analysis (see chapter 2)	Significant association with development of NCI CTC grade 3-4 CIPN	OR 13.98 (3.17-61.75, $I^2$0%) see meta-analysis in chapter 2	
CYP2C8*3	Abraham 2014(274)	No significant association	HR 1.13 (0.92-1.41, p=0.27)	The variant allele is known to be related to lower CYP2C8 activity of which the taxanes are known substrates
	Baldwin 2012(82)	No significant association	NS	
	Bergmann 2011(336)	No significant association	NS (p= 0.98)	
	Bergmann 2012(318)	No significant association	NS (p=0.46)	
	Boso 2014 (344)*	No significant association	NS	
	DeGraan 2013 (361)	No significant association	NS	
	Green 2008 (29)	Association with increased risk of motor neuropathy	NS (p=0.034)	
	Hertz 2012 (330)	Non-significant association for development of NCI CTC grade 3-4 neuropathy	OR 3.13 (0.89-11.01, p=0.075)	
	Hertz 2013 (281)	Association with cumulative dose at NCI CTC grade 2-4 neuropathy	European- American cohort: HR per allele 1.93 (1.05-3.55, p=0.032) African American cohort: HR 3.3 (1.04-10.45, p=0.043)	
	Hertz 2014 (296)	Association with increased neuropathy of CYP2C8 low metaboliser phenotype	HR 1.722 (p=0.018)	
	Lamba (343)	No significant association	NS	
	Leskela 2011 (301)	Association with cumulative dose of paclitaxel to grade 2 neuropathy	HR per allele 1.72 (1.05-2.82, p=0.032)	
	Marsh 2007 (363)	No significant association	NS	
	Ofverholm 2010 (346)	No significant association	NS	
	Rizzo 2010 (337)	No significant association	NS (p=0.6664)	

EPHA4 rs17348202	Leandro Garcia 2013 (85)	Significant association with cumulative dose at NCI CTC grade≥2 CIPN	HR 4.85 (2.57-9.13, $p=1.02x10^{-6}$)	The product of *EPHA4* is an ephrin receptor which has been associated with neuronal regeneration after injury.
EPHA5 rs7349683	Baldwin 2012 (82)	Association with cumulative dose at NCI CTC grade≥2 CIPN in discovery set	HR 1.63 (1.34-1.98, $p=9.6x10^{-7}$) in discovery set.	The product of *EPHA5* is an ephrin receptor which has been associated with neuronal regeneration after injury.
	Leandro- Garcia (85)	Association with cumulative dose at NCI CTC grade≥2 CIPN Meta-analysis evidence of significant association with cumulative dose at NCI CTC grade≥2 CIPN	HR 1.83 (1.32-2.55, $p=3.33x10^{-4}$) HR 1.68 (1.42-1.99, $p=1.4x10^{-9}$)	
EPHA6 rs301927	Leandro-Garcia 2013 (85)	Association with cumulative dose at grade≥2 CIPN	HR 2.35 (1.57-3.53, $p=3.44x10^{-5}$)	The product of *EPHA6* is an ephrin receptor which has been associated with neuronal regeneration after injury.
FGD4 rs10771973	Baldwin 2012 (82)	Association with cumulative dose at grade≥2 CIPN	HR 1.57 (1.3-1.91, $p=2.6x10^{-6}$) in exploratory cohort and replicated in validation sets	*FGD4* polymorphisms are associated with effects on development or maintenacne of Schwann cell function and are associated with congenital peripheral neuropathy(364, 365)
XKR4 rs4737264	Baldwin 2012 (82)	Association with cumulative dose at grade>2 CIPN	HR 1.68 (1.36-2.09, $p=1.9x10^{-6}$) in discovery set; HR1.84 (1.02-3.33, p=0.021 in European replication set. HR 1.23 (0.69-2.21, p=0.24) in the African American replication set	Protein product expressed in the cerebellum and frontal lobe and associated with attention deficit and hyperactivity disorder(366) and sensitivity to schizophrenia medications (367)
	Leandro- Garcia (85)	Association with cumulative dose at grade≥2 CIPN	Meta-analysis between two GWAS; HR 1.71 (1.41-2.06, $p=3.11x10^{-8}$)	

*studies were published after SNP selection and so weren't considered during the SNP selection process for the current study.

Two genome wide association studies performed in patients who had received paclitaxel chemotherapy were published in 2012 (82) and 2013 (85) , respectively. Baldwin et al. studied a large cohort of paclitaxel- treated breast cancer patients (82). Of the top hits in the exploratory cohort, one SNP reached significance in the Caucasian and African American replication sets. This SNP (*rs10771973*) lies in the *FGD4* gene, a gene that is associated with congenital peripheral neuropathy and in the exploratory cohort demonstrated a hazard ratio of 1.57 (95% CI 1.3-1.91, $p=2.6 \times 10^{-6}$) in the cumulative dose to grade 2 neuropathy analysis. Their top hit in the exploratory

analysis was in the *EPHA5* gene (*rs7349683*), the product of which has been associated with neuronal regeneration after injury. However, this association was not replicated in the validation cohorts.

Leandro-Garcia et al performed their GWAS in 144 patients treated with paclitaxel 175mg/m^2 three-weekly for any solid neoplasia (85). They did not identify any SNPs which crossed the threshold for genome wide significance; however interestingly amongst their top hits (p values $<10^{-5}$) it was notable, given Baldwin's findings, that a SNP in *EPHA4* was present (rs17348202, HR 4.85, 95%CI 2.57-9.13, p=1.02 x 10^{-6}) and a SNP in *EPHA6* featured amongst the top hits *(rs301927*, HR 2.35, 95%CI 1.57-3.53). Their results for rs1159057 in EPHA5, which is in high linkage equilibrium with Baldwin's *EPHA5* SNP, showed a HR of 2.01 (95% CI 1.43-2.84, p= 6.84 x10^{-5}). Their group performed meta-analysis of their own and Baldwin's results and both *rs7349683* and *rs4737264* in the *XKR4* produced results which crossed the genome wide significance level (HR 1.68, 95%CI 1.42-1.99, p=1.42 x 10^{-9} and HR 1.71, 95% 1.41-2.06, p=3.11 x 10^{-8}).

From the results of the systematic review, these findings were amongst the most interesting and appeared to warrant attempted replication. We therefore planned a candidate gene study to investigate an association of the SNPs listed in table 4.2 with the development of clinically significant sensory peripheral neuropathy in a cohort of taxane-treated patients.

Table 4.2. List of candidate SNPs to be investigated in the taxane-treated cohort

Gene	rs number	Chr position (bp)	Allele nomenclature	Amino Acid Substitution	Functional Consequence
CYP3A4	*rs35599367*	7:99768693	*22	n/a	↓activity (27, 368)
CYP2C8	*rs10509681* *rs11572080*	10:95038992 10:95067273	*3	p.K399R p.R139K	↓activity (369, 370)
EPHA4	*rs17348202*	2:221207458		n/a	Unknown effect of SNP; however EPHA4 is known to play an important role in the development of the nervous system including axonal guidance (371) and neuronal repair after injury (372-375)
EPHA5	*rs7349683*	4:66197804		p.G996G (NP_001268694.1)	Not known but almost exclusively expressed in the nervous system (376) and plays a role in axon guidance (377).
EPHA6	*rs301927*	3:97346618		intronic	Not known but part of the same family of molecules as EphA4 and EphA5
XKR4	*rs4737264*	8:55198762		intronic	Not fully understood and protein not well characterised, expressed in the cerebellum and thus far associated with ADHD (366) and risperidone response(367)
FGD4	*rs10771973*	12:32640040		intronic	Specific point mutations have been associated with congenital peripheral neuropathy CMT (364, 365)

Tables compiled with reference to dbSNP (378) and PharmGKB (379) databases
ADHD= Attention deficit and hyperactivity disorder
CMT= Charcot Marie Tooth disorder

4.1.2 Oxaliplatin study

From the systematic review, it was clear that oxaliplatin was the most studied drug in terms of investigating the association with CIPN. A number of candidate gene studies have investigated possible associations with genetic variants which may interfere with the metabolic pathways of platinum drugs. However, many of these have been contradictory. From data collected through the systematic review, meta-analysis was carried out where sufficient information was given in the study for inclusion. Overall, these analyses of many genetic associations including those of *GSTP1, GSTM1, GSTT1, ERCC1* and *2* and *XRCC1* showed no clear association. Rather than repeat these investigations in our study we elected to review the results of genome wide associations performed investigating oxaliplatin- induced peripheral neuropathy outcomes.

Two GWA studies have been carried out in this field. Neither revealed SNPs which crossed the generally accepted significance level for GWAS, but one did reveal a number of SNPs which were significantly associated with neurotoxicity at the $<10^{-5}$ level in their discovery cohort. This study involved 96 and 247 Korean patients in discovery and replication sets, respectively. They were treated with oxaliplatin and association was sought for those who experienced > grade 2 neuropathy or those experiencing grade 2 chronic neuropathy for >7 days. They identified nine significant SNPs; the most significant association that they observed was in *TAC1 (rs10486003)* with an odds ratio of 0.17 (95%CI 0.07-0.42, p= 2.04×10^{-5}). This association was replicated in the validation set with a combined OR of 0.32 (95%CI 0.19- 0.52, p=4.84×10^{-7}) The *TAC1* gene encodes four members of the tachykinin family, including substance P, which are thought to act as neurotransmitters. Four other SNPS were found to be significant in a multiple regression analysis (*rs2338, rs830884, rs843748* and *rs797519*)(272). In total 9 SNPs, significant at the $<10^{-5}$ level in the discovery set, showed association in the replication set.

A retrospective study in a Japanese population of 70 colorectal cancer patients treated with modified FOLFOX6 attempted to further explore the top nine hits from the Korean

GWAS (94). They used the same criteria for defining a 'case' of neurotoxicity. The study was limited by its retrospective nature but measures were put in place to aim for consistency in assessing the phenotype of patients. In a univariate analysis, they found that two of the nine GWAS-identified SNPs appeared to be significantly related to the development of neuropathy, *rs843748* in *ACYP2* and *rs17140129* in *FARS2*. The SNP in *FARS2* remained significant in multiple logistic regression analysis (OR 6.5, 95%CI 1.2-35.7, p=0.034). The top SNP in the GWAS, *rs10486003* in *TAC1,* whilst not shown to be related to the risk of development of neuropathy in the Japanese study, did appear to be significantly associated with the time to the onset of grade 1 chronic neuropathy.

These results appeared of potential interest but they were yet to be investigated in a Caucasian population. In our population of Caucasian individuals of European ancestry, we planned a candidate gene study to investigate possible associations with chronic oxaliplatin induced peripheral neuropathy and *rs843748 (ACYP2*), *rs17140129 (FARS2*) and *rs10486003 (TAC1*).

Table 4.3 Summary of details of SNPs selected for exploration in the oxaliplatin cohort

Gene	rs number	Chr position (bp)	Amino Acid Substitution	Functional Consequence
ACYP2	*Rs843748*	2:54502912	Intronic variant	Uncertain. ACYP2 encodes acylphosphatase 2 which is related to Ca^{2+}/Mg^{2+}-ATPase pump associated with skeletal muscle (380) and variants have also been linked to cisplatin ototoxicity (381)
FARS2	*Rs17140129*	6:5298362	Intronic variant	Uncertain. The protein product plays a role in mitochondrial protein translation. Mutations in this gene can result in encephalopathy (380)
TAC1	*Rs10486003*	7:97229778	n/a	This gene encodes four products of the tachykinin peptide hormone family which are thought to function as neurotransmitters which interact with nerve receptors and smooth muscle cells (380).

Tables compiled with reference to dbSNP(378) and PharmGKB (379)databases

4.2 METHODS

4.2.1 Patients and Methods

Two studies contributed to the total population for genotyping. The first was a prospective cohort of patients recruited at the beginning or during chemotherapy. Both studies were approved by the Liverpool ethics committee and all patients signed a consent form after being provided with information about the study (See appendix 1 for study protocols and ethics approval).

Inclusion criteria were:

(1) Patients over 18 years of age

(2) Due to commence/ receiving chemotherapy with one of the following regimens:

   a. Paclitaxel 175mg/m^2 three- weekly with or without concurrent three-weekly carboplatin (at least 4 cycles planned) or equivalent

   b. Docetaxel 100mg/m^2 for at least 4 planned cycles or at least 6 planned cycles of docetaxel 75mg/m^2.

   c. Oxaliplatin 85mg/m^2 or greater for at least 6 planned cycles

Exclusion criteria were:

(1) Patients with pre-existing peripheral neuropathy symptoms

(2) Patients receiving concurrent cisplatin or vinca alkaloid due to their known neurotoxic potential.

Patients were monitored by their own medical team and assessed each cycle by a chemotherapy nurse who scored the patients neuropathy according to the NCI CTC scale. In addition to these routine assessments, patients were clinically assessed by a member of the CIPN study team, and sensory and motor neuropathy graded according to the NCI CTC scale on or before the first day of cycle one, cycle four, post cycle 6 and post completion of treatment (for those receiving more than six cycles of chemotherapy).

Prospectively recruited patients who discontinued the planned course of chemotherapy early without meeting case criteria, who did not reach the minimum dose criteria to be classed as a control, were excluded from genotyping analysis. Examples included patients who discontinued paclitaxel due to hypersensitivity reactions after one or two cycles, or those who stopped chemotherapy due to disease progression on an interval scan. All prospectively recruited patients were also asked to complete EORTC-QLQ C30 and CIPN20 quality of life modules at recruitment, at cycle four, post cycle 6 and post completion of treatment (for those receiving more than six cycles of chemotherapy). They were also asked to again complete the same quality of life modules at 6 and 18 months post-completion of treatment.

The second study was a case-control study performed as part of the Molecular Genetics of Adverse Drug Reactions NIHR portfolio study. Patients were recruited through two sites, Clatterbridge Cancer Centre NHS Foundation Trust and St Helens and Knowsley NHS Trust. Eligible patients were identified either on the Chemotherapy Day Units where they received their treatment, notified to the trials team by patients' consultants or via lists of patients who had received the appropriate chemotherapy drugs generated by the coding department.

Inclusion criteria were:

(1) Patients over 18 years of age

(2) Meeting the case or control definition

Case definition: developed grade 3-4 CIPN during or within 6 weeks of completion of taxane or oxaliplatin chemotherapy OR have developed grade 2 neuropathy resulting in dose delay, dose reduction or early cessation of their taxane or oxaliplatin therapy.

Control definition: experienced no neuropathy or mild (maximum NCI CTC grade 1) neuropathy only.

(3) Had completed a course of chemotherapy including

(a) Paclitaxel 175mg/m^2 three- weekly with or without concurrent three-weekly carboplatin (at least 4 cycles planned) or equivalent

(b) Docetaxel 100mg/m^2 for at least 4 planned cycles or at least 6 planned cycles of docetaxel 75mg/m^2.
(c) Oxaliplatin 85mg/m^2 or greater for at least 6 planned cycles

Exclusion criteria were:

(1) the presence of any pre-existing peripheral neuropathy symptoms, or
(2) subsequent treatment with a further neurotoxic chemotherapy agent which could hamper assessment of severity or persistence of CIPN caused by the index drug course.

Medical case-notes and chemotherapy nursing records were reviewed to assess documentation of neuropathy during and after chemotherapy but patients were only recruited after a consultation with an experienced CIPN research practitioner to confirm NCI CTC grading of neuropathy. Case-notes alone were not relied upon due to the well-recognised fact that neuropathy is frequently under-recognised in routine practice.

For cases, patients must have experienced grade 3-4 CIPN or have developed grade 2 neuropathy resulting in dose delays, dose reductions or early cessation of their taxane or oxaliplatin therapy. Controls had to have completed a course of chemotherapy comprising at least 4 cycles of paclitaxel 175mg/m^2 given three-weekly; at least 4 cycles of docetaxel 100mg/m^2; at least 6 cycles of docetaxel 75mg/m^2; or at least 6 cycles of oxaliplatin 85mg/m^2. This was to ensure that anyone being categorised as a control had had a sufficiently high cumulative dose of taxane or oxaliplatin to feel confident that they represented an appropriate control rather than simply not having received enough of the drug. They had to have experienced a maximum of grade 1 neuropathy with no adjustment to their taxane therapy required for neurotoxicity. Particular care was taken when evaluating oxaliplatin-treated patients to ensure that both acute and chronic neuropathy symptoms were assessed and that it was the chronic neuropathy grading that contributed to their eligibility criteria for the study.

For all patients recruited through both studies, demographic data were collected along with clinical history of diabetes, alcohol excess or other conditions which could independently pre-dispose to neuropathy. Treatment details were recorded, including any dose delays, reductions or early cessation with reasons for any changes to planned schedule and importantly, the cumulative dose of taxane/ oxaliplatin received was recorded.

A 9ml EDTA blood sample was taken from each subject. If venepuncture was not possible a saliva sample was taken.

4.2.2 DNA extraction and genotyping

DNA was extracted from whole blood using chemagen kits. If for any reason it wasn't possible to collect a blood sample, a saliva sample was taken and DNA extracted using DNA Genotek Oragene DNA kits. DNA was quantified using Nanodrop™. The samples were then normalised and plated onto 96-well plates. All selected SNPs were confirmed to have a minor allele frequency >5% in Caucasian populations using HapMap prior to proceeding.

Taxane genotyping

Primers were obtained from Metabion (Planegg, Germany). Details of forward, reverse and extension primers are provided in table 4.4. The samples were genotyped using iPLEX chemistry on the MAssArray platform according to the manufacturer's instructions (Agena Bioscience GmBH, Hamburg, Germany) on mixed plates of cases and controls to ensure genotyping was performed blinded to clinical data. Any samples with a genotyping rate of <75% (6/8 SNPs) were to be excluded, as were any SNP assays with a call rate of <97%. 98 (50%) samples were analysed in duplicate to ensure quality and consistency of genotyping data.

Table 4.4. Details of forward, reverse and extension primers

	Forward primer (5' -3')	Reverse primer (5' -3')	Extension primer (5' -3')
rs35599367	ACGTTGGATGCTCCTTGATCTCAGAGGTAG	ACGTTGGATGCAGAAGGTGTTATCAGGTGC	CTCCATCACACCCAG
rs11572080	ACGTTGGATGTTTCTCCCTCACAACCTTGC	ACGTTGGATGCAGTGAGCTTCCTCTTGAAC	ACGGTCCTCAATGCTC
rs10771973	ACGTTGGATGGATGGCGATTTTTCTTCCCC	ACGTTGGATGACCCAAATCAGCTAGGACTC	GCTAGGACTCAGAGACA
rs10509681	ACGTTGGATGCTTATCTAGAAAGTGGCCAG	ACGTTGGATGTGGCATTACTGACTTCCGTG	gCGTGCTACATGATGACA
rs7349683	ACGTTGGATGATACCGGCCCATCTTGATTG	ACGTTGGATGATTGGCAGAACATAGCCCAC	CACCTACTGATCTGTAGGC
rs17348202	ACGTTGGATGCAAAATTCTTAGGTTCCCACG	ACGTTGGATGCATGTGACAAGTGGCTGTCG	TTGGATATCAGGATCTAGAG
rs301927	ACGTTGGATGGACAGAAAGGGAAACATCTC	ACGTTGGATGGAGATTTTTAAAAGGTCTTC	TAGCCAAATATGAGAATCATTG
rs4737264	ACGTTGGATGTCATTACAATGTGAATGGC	ACGTTGGATGAAGGATTCTGGCTATCACCC	ACCCACTATTACAGGGTTGTATAT

Oxaliplatin genotyping

Genotyping for the three selected SNPs was carried out using pre-validated, commercially available TaqMan real-time PCR allelic discrimination assays (LifeTechnologies, Paisley, UK) on mixed plates of cases and controls to ensure genotyping was performed blinded to clinical data. Any samples with more than one SNP result missing was planned for exclusion. Any SNP assays with a call rate of <97% were planned for exclusion. 18 samples (15%) were analysed in duplicate to assess genotype concordance.

4.2.3 Statistical analysis

The primary outcome investigated was an association of the selected SNPs with the occurrence of grade 3 or 4 sensory neuropathy, or grade 2 sensory neuropathy associated with dose delays, dose reductions or early cessation of taxane therapy. Potential clinical covariates were analysed between cases and controls prior to proceeding to genotyping analysis using SPSS (version 22). Age and BMI were compared using a student t test and cumulative dose of either paclitaxel/ docetaxel or oxaliplatin were compared between case and control groups using Mann Whitney tests. Status with regard to diabetes, alcohol consumption, concurrent medication with selective serotonin reuptake inhibitor (SSRI) or SNRI, gabapentin or pregabalin, calcium channel

blocker, or amitriptyline and prior taxane exposure were compared using chi square and Fishers exact tests. For oxaliplatin only, 2-weekly versus 3-weekly schedule was also compared using the chi square test.

Univariate analysis was carried out for SNP association with case or control status. Any clinical factors found to differ significantly ($p<0.1$) between case and control groups were then entered into the analysis (backward selection procedure). An exception to this was difference in cumulative dose for taxane patients. All control individuals had received a set minimum course of the drug as outlined above in the inclusion criteria and group comparisons were performed to confirm sufficient cumulative dose. Both docetaxel and paclitaxel-receiving patient control groups had received significantly more of the index drug than the case group. This can be accounted for by the fact that many of the case patients had had dose reductions or early cessation of their taxane due to their susceptibility to neurotoxicity. Cumulative dose was included in the oxaliplatin multivariate analysis as although minimum dose criteria were applied it was evident that cases had received a higher median cumulative dose of oxaliplatin.

Genotyping data was analysed with PLINK software using a logistic model and assuming an additive mode of inheritance. A Bonferroni p-value threshold of 0.00625 was set for the taxane study and 0.017 for the oxaliplatin study to account for multiple testing. For the patient reported outcome data (EORTC QLQ C30 and CIPN20 modules), all quality of life data were scored as per the EORTC guidelines. End of treatment CIPN20 sensory scores were compared according to case or control status using the Mann Whitney U test within SPSS (version22).

As a number of different SNP associations were being investigated no single sample size or power calculation is possible as the power to detect a significant difference in risk conferred by an individual SNP will vary depending on the effect size and the minor allele frequency. The aim was to recruit as many patients as possible within the study time period.

4.3 RESULTS

4.3.1 Taxane study results

A total of 193 eligible Caucasian patients of European background were recruited. Six patients were excluded from the genotyping for quality control reasons leaving 187 patients with valid genotyping data. All eight SNPs had call rate >99%. Four samples were excluded due to <75% successful genotyping, of which one sample had a particularly low concentration of DNA. Two samples were excluded due to non-concordance on duplicate genotyping (for each of these two duplicated samples, one of the eight SNPs was non-concordant, in each, one sample of the pair was called as a heterozygote and one as a homozygote wild-type for both pairs). Both of these samples were excluded from all SNP analysis. All SNPs were confirmed to be in Hardy Weinberg equilibrium (HWE) (p values all >0.2).

For the 187 patients included, there were only four missing genotypes; genotyping was successful for all but two SNPs in two samples. Both of these samples had low DNA concentration (9.725ng/ul and 44.82ng/ul, respectively) and this may therefore have contributed to the less than complete genotyping.

As a means of checking for clear genotyping errors or inconsistencies between the study population and the general population, where data was available, the study genotype frequencies were compared to those published through the HapMap-CEU (Utah residents with Northern/ Western ancestrory) population stated on the dbSNP database (378). This data is presented in table 4.5. For all except one SNP, there was no significant difference between our genotyping frequencies and those reported in the reference population. For the one SNP, the difference was due to the greater proportion of heterozygotes seen in the reference population compared to wildtype homozygotes for *rs7349683,* compared to our population.

Table 4.5 Genotyping distributions compared to other Caucasian populations (using HapMap- CEU genotype frequencies)

Rs number	Allele (ref/var)	Study population genotype data				Public data (n=no. of patients)	Chi square test p value Study data vs public data)
		A1/A1	A1/A2	A2/A2	MAF*	MAF*	
rs35599367	C/T	160	25	0	0.00675	0.025 (60)	n/a (MAF available only)
rs11572080	G/A	142	41	3	0.126	0.1083 (60)	p=0.66
rs10509681	T/C	142	41	3	0.126(C)	0.1372 (C) (n=113)	p=1.00
rs10771973	G/A	105	69	13	0.254 (A)	0.281 (A) (n=112)	p=0.806
rs7349683	C/T	92	75	20	0.3074	0.4027 (n=113)	**p=0.00**
rs17348202	T/C	164	22	0	0.0591	0.0575 (n=113)	p=1.00
rs301927	A/G	135	48	4	0.150	0.1637 (n=113)	p=0.841
rs4737264	A/C	105	69	13	0.2540	0.2389 (n=113)	p=0.564

*MAF=mean allele frequency

Demographic data for the eligible recruited patients are shown in table 4.6. Median age was 60.3 years. There was no significant difference in concurrent diabetes or alcohol consumption between cases or controls, and neither was there a difference in age or BMI. There was a significantly greater proportion of female patients in the case group. This is likely because paclitaxel causes more neuropathy than docetaxel and all of the paclitaxel- receiving patients were female in this cohort.

Table 4.6. Demographic and clinical details of the taxane- treated cohort

		Population N=193	Controls N=124	Cases N=69	P value where appropriate
Age (years)		60.3	59.9	61.0	P=0.486 ◊
Gender	Female Male	157 36	**94** **30**	**63** **6**	**P=0.008** †
Drug	Docetaxel Paclitaxel	101 92	**74** **50**	**27** **42**	**P=0.006** †
BMI		26.75	26.49	27.21	P=0.467 ◊
Diabetes	No Yes	187 6	122 2	65 4	p=0.188 ≠
Alcohol consumption	<1 unit per week 1-14 units per week 15-21 units per week >21 units per week Missing	95 75 5 3 15	57 52 4 2 9	38 23 1 1 6	p=0.544 †
Prior taxane treatment	No Yes Missing	181 10 2	115 8 1	66 2 1	p=0.499 ≠
Concurrent SSRI or SNRI	No Yes	175 18	111 13	64 5	p=0.449 ≠
Concurrent amitriptyline	No Yes	186 7	122 2	64 5	p= 0.100 ≠
Concurrent gabapentin or pregabalin	No Yes	188 5	121 3	67 2	p=1.00 ≠
Concurrent calcium channel blocker	No Yes Missing	173 19 1	113 10 1	60 9	p=0.282 †
Cumulative dose (mg/m^2)	Docetaxel Paclitaxel	467.6 888.2	483.4 996.2	424.3 759.1	p=0.04◊ p=0.00 ◊

†= chi square, ≠ = Fishers test, ◊= Mann- Whitney U test

None of the seven variants were found to be associated with development of taxane induced peripheral neuropathy on univariate analysis or after adjustment for

potentially relevant clinical factors (table 4.7). Study of docetaxel and paclitaxel- treated groups separately also showed no clear evidence of association (table 4.8).

Table 4.7. Genotyping results for taxane-treated cases and controls with effect estimates

Gene	SNP		Taxane			
			Controls	Cases	OR (95% CI)	p value
CYP2C8	****3***	*1/*1 *1/*3 *3/*3 Missing	92 26 1 0	50 15 2 1	1.25 (0.67-2.34)	0.484
CYP3A4	****22 (rs35599367)***	CC CT TT Missing	105 13 0 1	55 12 0 1	1.78 (0.76-4.16)	0.184
EPHA4	***rs17348202***	TT CT CC Missing	105 13 0 1	59 9 0 0	1.24 (0.50-3.08)	0.638
EPHA5	***rs7349683***	CC CT TT Missing	58 49 12 0	34 26 8 0	1.00 (0.64-1.56)	0.992
EPHA6	***rs301927***	AA AG GG Missing	87 31 1 0	48 17 3 0	1.18 (0.67-2.10)	0.553
FGD4	***rs10771973***	GG GA AA Missing	68 44 7 0	37 25 6 0	1.17 (0.73-1.88)	0.521
XKR4	***rs4737264***	AA AC CC Missing	69 42 8 0	36 27 5 0	1.17 (0.73-1.88)	0.521

Table 4.8. Genotyping results for taxane-treated cases and controls stated separately for docetaxel- and paclitaxel treated patients, respectively

Gene	SNP		Docetaxel		Paclitaxel	
			Controls	Cases	Controls	Cases
CYP2C8	****3***	*1/*1	55	19	37	31
		*1/*3	16	6	10	9
		*3/*3	0	0	1	2
		Missing	0	1	0	0
CYP3A4	****22 rs35599367***	CC	64	21	43	33
		CT	8	4	4	8
		TT	0	0	0	0
		Missing	0	0	1	0
EPHA4	***rs17348202***	TT	65	22	41	36
		CT	7	4	6	5
		CC	0	0	0	0
		Missing	0	0	1	0
EPHA5	***rs7349683***	CC	32	11	26	23
		CT	30	12	19	14
		TT	10	3	3	4
		Missing	0	0	0	0
EPHA6	***rs301927***	AA	52	16	35	31
		AG	17	9	13	8
		GG	3	1	0	2
		Missing	0	0	0	0
FGD4	***rs10771973***	GG	38	13	32	24
		GA	31	10	12	14
		AA	3	3	4	3
		Missing	0	0	0	0
XKR4	***rs4737264***	AA	45	17	26	19
		AC	24	8	17	18
		CC	3	1	5	4
		Missing	0	0	0	0

4.3.2 Results for oxaliplatin study

A total of 120 Caucasian colorectal cancer patients were eligible for genotyping analysis, 78 males and 42 females with a mean age of 61 years (range 27-80). The demographic and clinical data for the patient cohort are detailed in table 4.9.

Table 4.9 Demographic data for the oxaliplatin cohort

		Population	Controls	Cases	
Gender	**Female**	**42**	**23**	**19**	**P=0.064 †**
	Male	**78**	**29**	**49**	
Age (mean)		61.0	62.4	59.9	P=0.175 ≠
BMI (mean)		27.14	27.12	27.15	P=0.976≠
Diabetes	Yes	13	7	6	P=0.418 †
	No	107	45	62	
Previous oxaliplatin	Yes	6	3	3	p-1.00 ≠
	No	114	49	65	
Frequency of oxaliplatin		83	38	45	P= 0.417 †
	2 weekly	37	14	23	
	3 weekly				
Alcohol consumption					P=0.227 †
	<1 unit per wk	61	23	38	
	1-14 units/wk	43	21	22	
	15-21 units/wk	4	0	4	
	>21 units/wk	6	3	3	
Concurrent treatment with a SSRI/SNRI	No	112	48	64	P=0.726 ≠
	Yes	8	4	4	
Concurrent treatment with gabapentin/pregabalin	No	118	50	68	P=0.186 ≠
	Yes	2	2	0	
Concurrent treatment with amitryptilline	No	118	52	66	P=0.505 ≠
	Yes	2	0	2	
Concurrent treatment with a calcium channel blocker	No	105	43	62	P=0.164 †
	Yes	15	9	6	
Cumulative dose oxaliplatin (mg/m^2) (mean)		**662.2**	**622.7**	**692.4**	**P= 0.067 ◊**

†= chi square, ≠ = Fishers test, ◊= Mann- Whitney U test

The cumulative dose achieved was slightly lower in the control group for oxaliplatin-treated patients although a mean dose of 622.7mg/m^2 represents a satisfactory exposure. For a small group of patients, despite meeting the control criteria for at least six cycles of oxaliplatin, their total dose fell below this arbitrary threshold of 510mg/m^2 due to dose reductions for non-neurotoxicity reasons. It may also be that they were more palliative treatment patients in the control group who often receive fewer cycles per course than adjuvant patients. In our trial population, men were significantly at higher risk of meeting criteria for a case for CIPN. Due to the relatively small size of the

sample and the mixed study design, it is difficult to know how significant this is. There was no significant difference in the cumulative dose received between males and females (642.9 compared with 688.5mg/m^2). There was also no difference in the schedules between gender groups.

With regard to genotyping, call rates for all three SNPs were >99%. For *rs843748* and *rs10486003* there was one missing genotype each. No samples had to be excluded for having more than one genotype missing. For one sample, the likely reason for missing genotype data was low DNA concentration from a saliva sample. One of the duplicated samples showed non-concordance in one SNP (*rs10486003*), one sample was called as a heterozygote and one as homozygote wild-type. This sample was excluded for all SNP analysis leaving a sample size of 119. As with the genotyped taxane- treated cohort, genotype frequencies were compared between our study and those published on the dbSNP database (378).

Table 4.10 Genotyping distributions compared to other Caucasian populations (using HapMap- CEU genotype frequencies)

Rs number	Allele (A1/A2)	Study population genotype data				Public data	Chi square test p value* Study data vs public data)
		A1/A1	A1/A2	A2/A2	MAF	MAF	
rs843748 (ACYP2)	A/G	32	49	37	0.5212	0.5417	P=0.767
rs17140129 (FARS2)	A/G	87	31	1	0.1387	0.1460	P=0.813
rs10486003 (TAC1)	C/T	91	26	1	0.1186	0.1018	P=0.860

*Exact 2 sided p value stated

There was no association seen with any of the three SNPs selected in our Caucasian population on either univariate analysis or on multivariate analysis (table 4.11).

Table 4.11 Genotyping results for oxaliplatin- treated patient cohort with effect estimates

SNP		Controls	Cases	OR (95% CI)	P value
rs843748 (ACYP2)	AA AG GG missing	15 20 16 0	17 29 21 1	0.93 (0.58-1.50)	0.778
rs17140129 (FARS2)	AA AG GG missing	36 15 0 0	51 16 1 0	0.87 (0.40-1.90)	0.734
rs10486003 (TAC1)	CC CT TT Missing	41 10 0 0	50 16 1 1	1.46 (0.63-3.39)	0.382

Since this work was carried out, an Italian group has also attempted this same replication in a Causcasian population (89). They elected to investigate eight SNPs from the original GWAS by Won et al in a population of 150 colorectal cancer patients. They also could not demonstrate an association with the GWAS-identified SNPs. Given that data was available from three of four studies investigating these three SNPs, the combined results were entered into a meta-analysis. The main limitation to this is the slightly differing case definition. Terrazzino et al used grade 2-4 chronic neuropathy, Oguri et al used grade 3-4 or grade 2 lasting more than 7 days and in our study, we used grade 3-4 chronic neuropathy or grade 2 chronic neuropathy resulting in adjustment to treatment regimen. But given that differences were small in the definitions, and all studies have used NCI CTC, it didn't seem unreasonable to look at the pooled data. Unfortunately, the genotype data per case/ control status was not published in the original GWAS (272), and so these data could not be entered into a RevMan meta-analysis. Also, the Oguri study did not state their odds ratios and so this study could not be entered into a QWAMA meta-analysis. Therefore, both meta-analyses were conducted by including three out of four studies. The forest plots from RevMan meta-analysis are presented below in figure 4.1. The results from meta-analysis using QWAMA are presented in table 4.12.

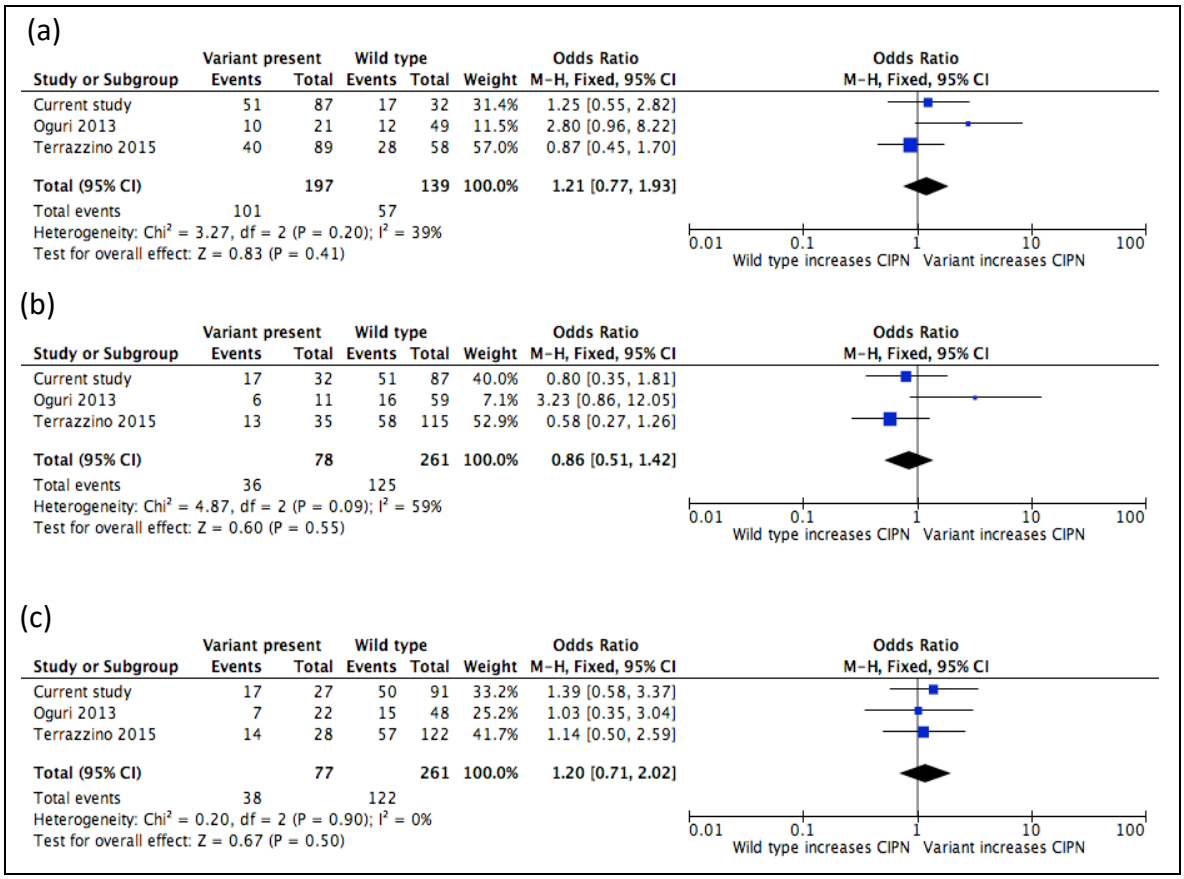


Figure 4.1. Forest plots showing pooled data from studies investigating a*) rs843748 (ACYP2*) b) *rs17140129 (FARS2*) and c)*Rs10486003 (TAC1)*

Table 4.12 QWAMA meta-analysis; pooling odds ratios from eligible studies investigating association with GWAS- identified SNPs

Rs number	**OR (95% CI)**	**Z**	**p-value**
Rs843748	2.21 (1.72-2.86)	6.11	1.02E-009
Rs17140129	1.17 (0.81-1.70)	0.85	0.40
Rs10486003	0.67 (0.46-0.99)	-2.04	0.04

For the *ACYP2* SNP our results agree with the direction of risk of the variant allele found by the Asian studies albeit in a non-significant way, whereas for the *FARS2* variant which was associated with an OR of 14.45 in the original GWAS, both studies in Caucasian populations do not even suggest a trend in this direction. For *TAC1* the results in all three studies look very similar. Oguri et al demonstrated an association with time to onset of CIPN with this variant rather than an association with development of marked CIPN symptoms (94). In the original GWAS, this variant was protective with an OR 0.17. The QWAMA analyses are highly skewed by the Won data (272).

4.3.3 Patient reported outcomes

Patient reported outcomes as summarised by the EORTC CIPN 20 sensory scores were compared between cases and controls to test confidence in phenotyping for this subjective adverse effect. Patient reported outcomes were only available for the prospectively recruited patients but provide extra information for a sample of patients. CIPN20 results were available for a total of 88 genotyped patients (49 controls and 39 cases). There was no significant difference in the sensory or motor scores at baseline but were numerically slightly higher in the control group (p=0.57 and 0.78 for sensory and motor scores, respectively). At all other time points, the case group scored higher and p values for the difference in scores are presented in table 4.12. All are significant demonstrating that our phenotypic classification is supported by patient reported outcomes.

Table 4.13. p values demonstrating significant differences in CIPN20 sensory and motor scores at all time points throughout assessment up to 18 months post-completion of chemotherapy

Group	N	P value (after 6 cycles sensory score)	P value (after 6 cycles sensory score)	N	P value (after 6 cycles sensory score)	P value (motor score after 6 cycles)	No of patients	P value (sensory score 6 months post-chemo)	P value (motor score 6 months post-chemo)	Number of patients	P value (sensory score 18 months post-chemo)	P value (motor score 18 months post-chemo)
Controls	47	0.000	0.008	49	0.000	0.000	36	0.000	0.017	25	0.032	0.041
Cases	25			39			22			18		

All p values are two sided and generated using the Mann Whitney U test to compare scores

4.4 DISCUSSION

In this study, designed to attempt replication of previous putative genetic associations with taxane and oxaliplatin induced peripheral neuropathy, we failed to demonstrate a significant association with any of the selected candidate SNPs. There was not even a suggestive trend in our data. This could be due to many reasons; Firstly, no association

may in fact exist. With the *CYP3A4*22*, the initial study that identified the association only found the association in female cohorts and the numbers of cases were very small (100). They looked at an association with NCICTC grade 3 neurotoxicity and the **22* variant using a dominant model. However, only two patients in the exploratory cohort and four patients in the validation cohort experienced grade 3 neurotoxicity. Our case definition was slightly different, but evaluation of our female paclitaxel group alone to compare with their analysis as closely as possible, still leaves us with no significant association (p=0.21). The proportion of patients with the variant allele was similar in both our and De Graan's study (15% and 14%, respectively). Whilst some studies of *CYP2C8*3* have shown an association, others have not, and our study adds weight to the negative studies. The other SNPs have been identified through GWAS and may be false positives. The paclitaxel genome wide studies also used a different outcome measure, cumulative dose to grade 2 neuropathy (82, 85). This outcome has been increasingly used in studies investigating CIPN and genetic risk. This has the advantage that it takes into account the dose received. However it does not take account those patients who may develop grade 2 or higher neuropathy at the end of treatment, who will have received the same dose as those who have not had any neuropathy throughout treatment. It is also not clear what happens to those patients who stop paclitaxel early due to other reasons. For oxaliplatin, perhaps the SNPs identified as potentially associated with oxaliplatin induced peripheral neuropathy are only relevant in an East Asian population or again perhaps they are purely false positives. In the original GWAS, although the SNPs looked promising particularly given their within-study and partial independent replication they did not meet the significance level generally accepted for genome wide studies, and this may offer an explanation as to why further studies have not been able to replicate the findings.

Secondly, an association may exist but the increased risk conferred by variant genotypes may be small and our study was simply not large enough to detect these differences. The size of our study is a weakness. A larger population would ideally be used to investigate this likely complex susceptibility trait.

There are however some strengths of our study. Despite the retrospective recruitment of a proportion of our patient cohort, all patients were specifically interviewed to confirm the history and details of chemotherapy induced peripheral neuropathy rather than relying purely on documentation in case notes. Care was taken in defining phenotyping to ensure controls had had sufficient exposure to ensure that the individual cumulative dose had reached a clinically relevant threshold. All paclitaxel patients received three weekly therapy with carboplatin achieving homogeneity of treatment. All docetaxel patients were treated on three weekly schedules at a dose of 60-100mg/m^2. All oxaliplatin treated patients were being treated for colorectal cancer in combination with a fluoropyrimidine, and two weekly or three weekly schedule was considered as a covariate. A more homogeneous cohort may have been achieved by specifying just one tumour group in one setting, i.e.. adjuvant or palliative, but that would have impacted on the sample size. Therefore, a balance must be achieved between the degree of standardisation of the studied population versus limiting the numbers recruited. A further strength of our study was using patient reported outcomes to support and validate health professional CIPN assessment and grading. With such a subjective toxicity, this is particularly important.

4.5 CONCLUSION

This was a candidate gene study for susceptibility based on a comprehensive systematic review of the evidence base to date. In neither the taxane, nor the oxaliplatin-treated groups, were the previously reported SNPs found to have a significant association with clinically important CIPN. Small study size was the main limitation and phenotypic characterisation the biggest strength. Since undertaking the study, other studies have agreed with the conclusions of this study, but new SNP associations have also been reported which may open avenues for further investigation. Building of a biobank of well-defined case and control subjects with patient reported outcome data to support categorisation has the potential to be an asset to continue to explore further potential associations. In the field of taxane-induced peripheral neuropathy, the Charcot Marie Tooth related genes (321, 322) warrant further investigation. For oxaliplatin, a large

GWAS may be necessary with well-defined phenotypic categorisation to generate new avenues for exploration.

CHAPTER 5

IMPACT OF CIPN ON QUALITY OF LIFE: CLINICAL COHORT STUDY

5.1 INTRODUCTION

There has been increasing focus in recent years on survivorship issues in cancer care. As a report by MacMillan Cancer Support identified, there are 500,000 people living with poor health or disability due to cancer or its treatment (382). Some of this number is certainly due to effects of incurable cancer and not all will be avoidable, but a significant number live with long term toxicity of treatment and understanding this better is vital to improve patient counselling, treatment, support and hopefully in the end, prevention. There are no good estimates of the prevalence of chemotherapy induced peripheral neuropathy. It has been shown that physicians underestimate CIPN symptoms (154) and there is relatively little published data documenting the impact of persistent CIPN. Although incidence data are available from clinical trials, CIPN is frequently reported as a largely reversible adverse effect. However, as mentioned previously, a small proportion of patients experience persistent symptoms and this may be under-estimated in clinical trials because of the nature of the follow which tends to be short-term. Indeed, experience from real-life populations supports the notion that long-term effects are more significant than previously reported.

A group exploring the experience of CIPN conducted a qualitative thematic systematic synthesis of the literature to understand the effect of this adverse reaction (383). They identified five studies which collectively evaluated 88 patients who had received neurotoxic chemotherapy. These studies described some of the functional impacts of CIPN, including effects on buttoning shirts, fastening jewellery, turning pages, walking, and climbing stairs. The studies also reported that patients had been unable to return to usual work duties and felt that socialising was inhibited.

A systematic review published in 2014 found only 11 studies which actually investigated a direct association between CIPN and quantitative measures of quality of life (384). Eight studies suggested a correlation (138, 152, 385-390) whereas three studies did not (391-393). Other studies included in the review, whilst not directly exploring the correlation between quality of life measures and CIPN, looked at both changes in

quality of life and CIPN, separately, over time. For instance, one prospective study demonstrated that EORTC QLQ-C30 QoL scores did not change over time whilst CIPN increased (394). Similarly, a number of randomised controlled trials reported differential rates of neurotoxicity between treatment arms but no difference in QoL (395, 396). The authors concluded that further prospective studies using validated questionnaires were necessary.

Table 5.1 Table of studies to date exploring a direct association between CIPN and QoL

Study	Population	Primary cancer and treatment	Design	CIPN assessment		QoL assessment tool	Conclusions
				Type of assessment	Tool		
Arraras et al (397)	39	Lung cancer; platinum doublets	Prospective	HCP	NCI CTC	EORTC QLQ-C30 EORTC QLQ-LC13	No significant association with low global QOL
Bayo et al (398)	92	Breast cancer; docetaxel, epirubicin, cyclophosphamide	Cross-sectional	Patient HCP	Toxicity questionnaire NCI CTC	Euro-QOL-5D	No evidence of association between CIPN and QOL
Calhoun et al (392)	99	Ovarian cancer; carboplatin and paclitaxel	Prospective	Patient HCP NP	FACT/GOG-NTX Sensory symptoms, pin prick sensation, power, reflexes, vibration test Thermal discrimination threshold test, vibration threshold test	FACT-G	No effect; FACT-G improved as FACT/GOG-NTX deteriorated
Cella et al (152)	230	Lung cancer; carboplatin and paclitaxel	Prospective	Patient	FACT/GOG-NTX, FACT-taxane	FACT-G	Significant decrease in total FACT-G scores with neurotoxicity but no correlation with change in global QoL
Driessen et al (390)	131 (43 pre-, 88 post-chemo)	Mixed tumour types treated with any potentially neurotoxic drugs	Cross-sectional	Patient	CINQ(399) FACT/GOG-NTX	FACT-G	Significant negative correlation with both FACT/GOG-NTX and CINQ with FACT-G scores
Griffith et al (388)	29	Mixed tumour types treated with taxanes or platinums	Prospective	Patient HCP Clinical NP	FACT/GOG-NTX, Neuropathic pain scale NCI CTC Pinprick sensation, reflexes Current perception threshold, quantative sensory testing, mechanical detection thresholds,vibration perception threshold, grip strength	FACT-G	Correlation between NCI CTC sensory grading and current perception threshold with inverse relationship between CPT and FACT/GOG-NTX and FACT-G total score
Hershman et al (400)	100	Early stage breast cancer; adjuvant taxanes	Mixed prospective and cross-sectional	Patient NP	FACT-GOG-NTX QST; tactile threshold and vibration threshold	FACT-G	Severe neuropathy associated with lower scores on the physical well being subscale of the FACT-G. FACT/GOG-NTX scores inversely correlated with hand vibration QST

Kim et al (387)	32	B-cell lymphoma; R-CHOP or R-CVP	Prospective	Patient HCP NP	Neuropathy symptom score and neuropathy disability score(401) NCI CTC NCS	SF-36	Significant reduction in physical function, social function, role function, bodily pain, vitality and physical component summary scores of the SF-36 in patients with neurotoxicty
Mols et al (385)	1643	Colorectal cancer; no chemo, oxaliplatin- based chemo and chemo without oxaliplatin	Cross-sectional	Patient	EORTC QLQ-CIPN20	EORTC C30	Those with many neuropathy symptoms reported significantly worse scores on all functioning and the global health status scale.
Morita et al (391)	377	Lung cancer; irinotecan with or without cisplatin or cisplatin and vindesine	Prospective	HCP	WHO guidelines	QOL-ACD(402)	No significant effect between peripheral neuropathy and the four domains of the QOL scale
Ostchega et al (389)	30	Testicular or ovarian cancer; cisplatin	Cross-sectional	Patient: research based symptom survey	Satisfaction with life scale(403) QoL questionnaire	Satisfaction with life scale(403) QoL questionnaire	CIPN associated with QoL
Padman et al (10)	25	Colorectal cancer; oxaliplatin	Cross-sectional (>2 years post chemo)	Patient HCP NP	Semi-structured interview and EORTC CIPN20 NCI CTC, mTNS Modified TNS	WHOQOL BREF EQ-5D-5L	Higher TNS score showed a trend towards poorer WHOQOL scores but was not significant. No significant correlation between self-reported neuropathy symptoms and functional impairment scores.
Song et al (404)	66	Haematology malignancies; vincristine, thalidomide, lenalidomide,or bortezomib	Cross-sectional study	Patient	EORTC CIPN20	EORTC QLQ-C30	CIPN-related lower limb extremity symptoms associated with global health status and functional scales of the EORTC QLQ- C30
Sorbe et al (386)	110	Ovarian cancer; Docetaxel and carboplatin	Prospective	Patient HCP Clinical and NP	Questionnaire NCI CTC Romberg test, patellar and Achilles reflexes, 2-point discrimination and vibratory sense.	EORTC QLQ-C30, EORTC OV28	Significant association between development of CIPN and global QoL
Tachi et al (405)	48	Breast cancer; treatment not stated	Prospective	HCP	NCI CTC	EQ-5D QOL-ACD	No significant association between peripheral neuropathy and quality of life
Tofthagen et al (406)	111	Colorectal cancer; oxaliplatin	Cross-sectional study	Patient	CIPNAT	SF-36	No effect on the general health measure of the SF-36 but association with worse outcome on all other subscales and higher scores for CIPN
Yoo et al (407)	195	Mixed; taxanes and or platinum	Cross-sectional study	Patient HCP	FACT/GOG-Ntx Power, reflexes, pinprick perception, vibratory perception	FACT-G	Weak negative associations between clinical findings associated with CIPN and various subscales of the FACT-G

HCP= health care professional, NP=neurophysiological.

There are several reasons why some studies may not have shown a correlation between CIPN and quality of life measures. For example, in Calhoun et al, the majority of the population with ovarian cancer had advanced disease; if they responded to chemotherapy, it is unsurprising that their quality of life may improve despite worsening CIPN given that their cancer symptoms may improve and they feel that treatment is having some success (392). In the Morita et al study, occurrence of peripheral neuropathy and QOL scores were assessed over the first four weeks of treatment only. Given that CIPN usually develops with higher cumulative doses over time, it is unsurprising that only a small number of patients experienced this side effect during the 4-week time period, and that the study showed no significant impact on QOL (391). In the Ramchandren study looking at 37 survivors of childhood acute lymphoblastic leukaemia, almost a third were found to have neuropathy on neurophysiological studies but most were asymptomatic, and thus no correlation was seen with overall quality of life (393).

Since the systematic review, a number of studies have been published. Padman et al performed a cross- sectional study of patients at least 2 years post initiation of oxaliplatin-based chemotherapy. They combined clinical and neurophysiological examination (nerve conduction studies) with the WHO quality of life scale and EQ-5D-5L health questionnaire to grade depression and the EORTC QLQ-CIPN20. They also interviewed all patients. Twenty-five patients participated although only 13 went ahead with neurophysiological tests. Two had pre-existing diabetic neuropathy. Out of the 25, three reported always having symptoms of CIPN, and six often had symptoms of CIPN. The main conclusions from the interviews were that a number of these patients felt inadequately warned about the possibility of such symptoms. A small number of patients were not able to continue working due to symptoms of CIPN. Overall however it seemed that they felt satisfied with the decision to receive the treatment (10).

A study relating questionnaire scores on the Functional Assessment of Cancer Therapy-Gynecologic Oncology Group- neurotoxicity subscale (FACT-GOG-Ntx) to a bedside assessment of CIPN by experienced nurses including vibration and light touch testing showed a weak correlation with negative quality of life scores. Patients reported that

'numbness or tingling in feet', feeling 'weak all over', 'numbness or tingling in the hands' and 'trouble buttoning buttons' had a severe, negative impact on their quality of life (407).

Tofthagen et al performed a cross-sectional study of 111 colorectal cancer survivors at 1-7 years post-initiation of chemotherapy using the Medical Outcomes Study Short Form 36 (SF-36) to measure health-related quality of life alongside a modified version of the 'Chemotherapy Induced Peripheral Neuropathy Assessment Tool (CIPNAT)' which measured both symptom severity and interference of symptoms with everyday activities (406). They demonstrated a correlation between poorer HRQOL and scores indicating increased CIPN symptoms and interference on the CIPNAT scales. They found no association between years since initiation of chemotherapy and scores on the CIPNAT suggested significant persistence of symptoms. However, the cross-sectional design could have introduced bias into the population. Patients with CIPN seven years after chemotherapy may be more motivated to participate and return questionnaires than those whose lives have returned to normal several years on.

Arraras et al looked at a prospectively recruited group of 39 patients during chemotherapy and follow up for non-small cell lung cancer. Whilst there was an increase in neuropathy through treatment, it was not considered to be a significant risk factor for low quality of life scores with fatigue being a bigger influence (397). Bayo et al performed a cross-sectional study of 92 breast cancer patients undergoing adjuvant or neoadjuvant docetaxel treatment. Whilst some adverse effects appeared to have a negative impact on quality of life, peripheral neuropathy was not significantly correlated with quality of life as measured by the Euro-QoL-5D (398). Tachi et al compared elements of the Euro-QoL-5D questionnaire before and after the first episode of chemotherapy for 48 patients with breast cancer. They noted a decrease in quality of life measures but this didn't appear to be significantly associated with the occurrence of peripheral neuropathy (405).

Only relatively few prospective studies have been performed and results have been contradictory. The tools used have varied widely. Quality of life and patient report tools were incorporated into the current project design both to support phenotypic characterisation for the pharmacogenetics study (Chapter 3) but also to further investigate a

link between occurrence and severity of CIPN and impact on quality of life measures both during chemotherapy but also at a set time distant to completion of chemotherapy.

5.2 METHODS

Patients aged 18 years old or over were invited to participate if they were commencing or were receiving chemotherapy with either at least four cycles of three-weekly taxanes (docetaxel or paclitaxel) or at least six cycles of oxaliplatin. All patients being treated through Clatterbridge Cancer Centre undergo a nurse-led pre-assessment appointment prior to commencing a course of chemotherapy. Pre-assessment appointments were screened on a weekly basis to identify patients attending who may be eligible. Chemotherapy clinic diaries were also screened regularly to check for eligible patients.

Patients were excluded if they had a history of peripheral neuropathy prior to starting the index course of chemotherapy. They were also excluded if they were receiving more than one drug with a high risk of neurotoxicity, for example, concurrent treatment with cisplatin was not allowed. All included patients completed a written consent form.

Patients were assessed at each cycle by a chemotherapy nurse. A toxicity proforma is routinely completed for all patients including an assessment of CIPN according to the NCI CTC criteria. CIPN was independently assessed by a member of the study team on cycle 4, after cycle 6 and after the final cycle (if patients were receiving >6 cycles of treatment).

Patients were asked to complete EORTC C30 and CIPN 20 forms at the start of their treatment, at cycle 4, after cycle 6 and after the final cycle (for patients receiving >6 cycles of chemotherapy). They were also sent the same questionnaires to be completed at six and at eighteen months after the completion of chemotherapy. Patients completed their questionnaires independently unless they specifically asked for help with either reading the questions or documenting their responses.

5.2.1. EORTC CIPN20 module

The CIPN20 scale was developed by the European Organisation for Research and Treatment of Cancer (EORTC) (155) and is used in conjunction with their main 30-item health-related quality of life module, the EORTC-QLQ C30. The 20 patient self-report questions relate specifically to symptoms of sensory, motor and autonomic neuropathy (table 5.2).

Table 5.2. EORTC CIPN-20 module

During the past week:				
	Not at all	A little	Quite a bit	Very much
Did you have tingling fingers or hands?[a]	1	2	3	4
Did you have tingling toes or feet?[a]	1	2	3	4
Did you have numbness in your fingers or hands?[a]	1	2	3	4
Did you have numbness in your toes or feet?[a]	1	2	3	4
Did you have shooting or burning pain in your fingers or hands?[a]	1	2	3	4
Did you have shooting or burning pain in your toes or feet?[a]	1	2	3	4
Did you have cramps in your hands?[b]	1	2	3	4
Did you have cramps in your feet?[b]	1	2	3	4
Did you have problems standing or walking because of difficulty feeling the ground under your feet?[a]	1	2	3	4
Did you have difficulty distinguishing between hot and cold water?[a]	1	2	3	4
Did you have a problem holding a pen, which made writing difficult?[b]	1	2	3	4
Did you have difficulty manipulating small objects with your fingers (for example, fastening small buttons)?[b]	1	2	3	4
Did you have difficulty opening a jar or bottle because of weakness in your hands?[b]	1	2	3	4
Did you have difficulty walking because your feet dropped downwards?[b]	1	2	3	4
Did you have difficulty climbing stairs or getting up out of a chair because of weakness in your legs?[b]	1	2	3	4
Were you dizzy when standing up from a sitting or lying position?[c]	1	2	3	4
Did you have blurred vision?[c]	1	2	3	4
Did you have difficulty hearing?[a]	1	2	3	4
Please answer the following question only if you drive a car				
Did you have difficulty using the pedals?[b]	1	2	3	4
Please answer this question only if you are a man				
Did you have difficulty getting or maintaining an erection?[c]	1	2	3	4

[a] sensory scale, [b] motor scale, [c] autonomic scale

Patients rate the degree of effect of specified symptoms on a Likert scale scored 1-4 where a score of one equates to 'not at all' and a score of 4 equates to 'very much'. As can be seen from the analysis plan below, autonomic scores were not utilised for this study as autonomic neuropathy is not commonly expected with the drugs involved in this cohort of patients.

5.2.2 Statistics

The primary aims of this study were two-fold; To investigate for an association between CIPN20 (sensory and motor neuropathy) score and global quality of life and functional score and to investigate the impact of persistence of changes following treatment.

Descriptive statistics were used to summarize sample characteristics and the patient reported outcomes measured by the EORTC QLQ C30 and the EORTC CIPN-20. It is important to note that for functional and global of quality of life measures a higher score indicates better outcomes and for the neuropathy elements and the symptom scores a higher score indicates greater symptom burden. For measures using the prospective data only, patients receiving three or more cycles were included rather than using an intention to treat population. This is because the primary outcome of interest is toxicity related rather than an efficacy outcome. For purposes of prospective, longitudinal analysis it was planned to explore the data based on two separate groups, paclitaxel and oxaliplatin, rather than as a whole due to the marked heterogeneity. For the whole group analysis, there were planned analyses of sensory and motor scores with functional and global quality of life scores using Spearman's rank test. Similar analysis was planned for exploration of correlation in the prospective paclitaxel and oxaliplatin groups, respectively.

For exploration of persistent neuropathy, those with scores ten points above mean baseline levels at 18 months post chemotherapy were categorised as having persistent neuropathy and these patients were compared with respect to functional scores to those whose neuropathy had resolved to mean baseline levels plus ten points or below at 18 months post chemotherapy completion. The cut-off of ten points above baseline was selected as this is there is evidence that a ten point difference in many symptom based scores in

cancer-related QOL scales is considered the lower estimate of a clinical meaningful medium effect (408, 409).

To explore correlation between NCI CTC grade and sensory score, mean sensory score was calculated at each time point and the means compared between groups using ANOVA.

5.3 RESULTS

5.3.1 Patients

In total, 162 patients were recruited to the quality of life study. After exclusions in the prospectively recruited cohort (see figure 5.1), 133 patients were left. The clinical characteristics of the total and prospective populations are detailed in table 5.2.

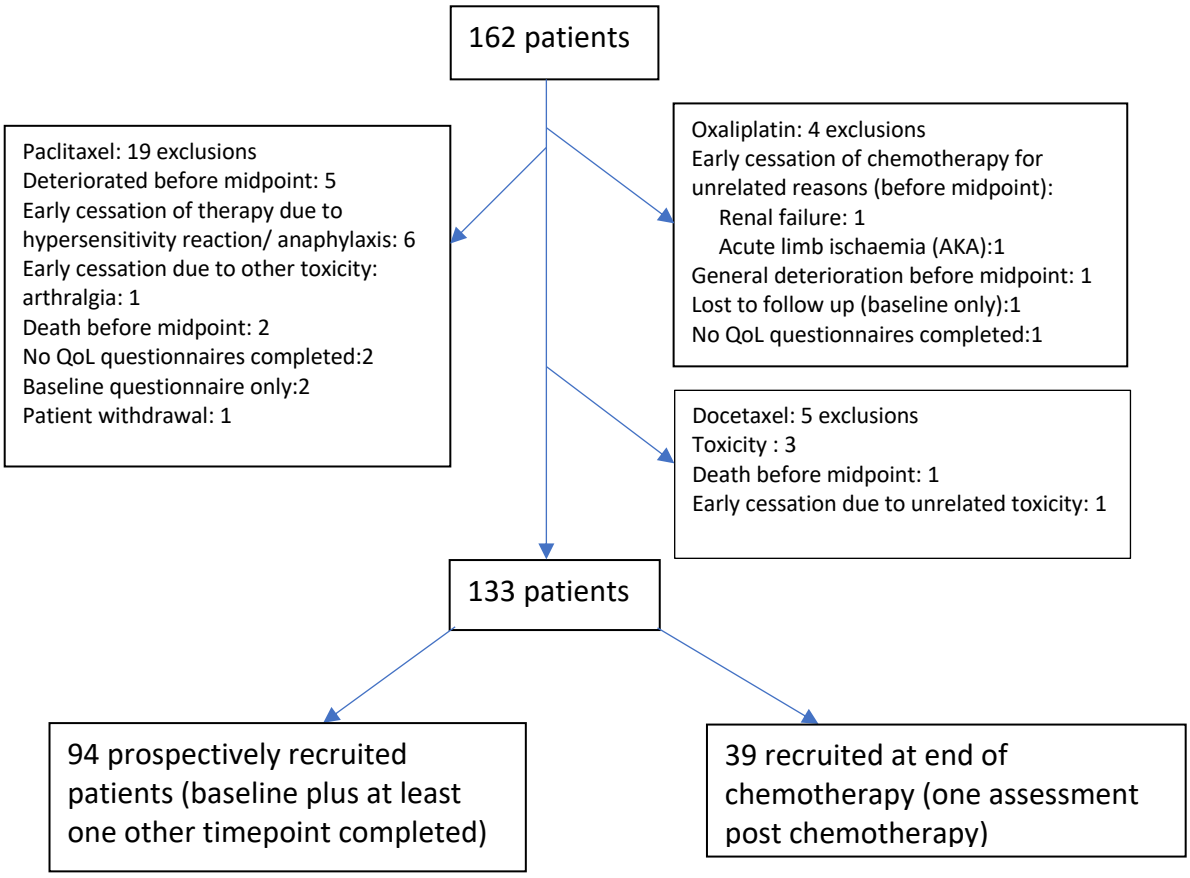


Figure 5.1 Flow diagram to show recruited patients and reasons for exclusion

Table 5.3. Characteristics of the study population as a whole and for the prospectively recruited patient cohorts

	Whole population (n=133)	**Prospective cohort (n=94)***	**Paclitaxel prospective cohort (n=48)**	**Oxaliplatin prospective cohort (n=34)**
Median age (range)	62 (43-80)	62.5 (43-80)	60 (43-80)	63 (48-77)
Males/ females	47M/ 86F	31M/ 63F	48 F	19 M/ 15 F
Primary cancer				
Colorectal cancer	49	34	0	34
Ovarian cancer	47	36	35	0
Primary peritoneal cancer or other gynae**	22	13	13	0
Prostate	15	12	0	0
Regimens				
Carboplatin/ paclitaxel	66	47	47	0
Carboplatin/ paclitaxel/Bev	2	1	1	0
Ox/MdG	17	12	0	12
Ox/MdG/ Bev	1	0	0	0
Ox/cape	24	16	0	16
Ox/cape/ Bev	2	0	0	0
XELOX	6	6	0	6
Docetaxel	15	12	0	0
Alcohol excess (>15 units per weeks)	15	11	1	7
Diabetes	6	4	2	2

*This number includes 48 paclitaxel treated patients, 34 oxaliplatin treated patients and 12 docetaxel treated patients
**uterus, cervix, fallopian tube
Ox: oxaliplatin, MdG:Modified de Gramont, Bev: Bevacizumab, Cape: capecitabine, XELOX: capecitabine and oxaliplatin

In the oxaliplatin prospective cohort, 34 patients completed a baseline questionnaire. Twenty-four patients completed questionnaires (71%) after 3 cycles and 24 (71%) after 6 cycles. Twenty patients received greater than six treatment cycles, 16 of whom completed questionnaires. Twenty-two patients (65%) completed 6 month follow up questionnaires, and 15 (44%) completed 18 month questionnaires. Reasons for not completing subsequent questionnaires included: lost to follow up; non-return of questionnaires, progressive disease or early cessation of treatment due to other reasons and death during the follow-up period.

For the paclitaxel prospective cohort, 58 patients were recruited, 48 of whom were included in the study. This was due to five patients discontinuing treatment after one or two cycles due to hypersensitivity reactions to paclitaxel, three patients stopped prior to midpoint assessment, two due to grade 3 fatigue and one due a general deterioration in condition. Two patients sadly died before cycle 3. 48 patients therefore had a baseline quality of life assessment and at least one further assessment. Forty-one patients completed the questionnaires after three cycles (midpoint; 85%) and forty at the post cycle six-time point

(83%). In the paclitaxel cohort, only one patient received >6 cycles and completed a further set of questionnaires at the end of treatment. Thirty patients completed questionnaires at six-month follow up (63%) and twenty-two at the 18-month post chemotherapy time point (46%). An additional 19 patients had data available for cross sectional study. Twelve docetaxel-treated patients were recruited prospectively and a further three were suitable for cross-sectional analysis.

At the six month time point, five patients in the oxaliplatin prospective cohort had commenced second line chemotherapy and three of the docetaxel patients had started second line therapy with abiraterone. At the 18-month follow up point, a further two of the oxaliplatin group had commenced second line therapy and a further two docetaxel patients were receiving further systemic anti-cancer therapy. At the six-month time point, none of the paclitaxel patients who returned their questionnaires were on subsequent lines of therapy but at the 18-month time point, three of the patients who returned questionnaires were on subsequent lines of therapy for progression of their cancer.

5.3.2 Analysis of the total study population

Figures 5.2 and 5.3 show scatter plots showing sensory and motor scores, respectively, plotted against both functional score and global quality of life scores at each time point post-baseline.

From visual inspection of these scatter plots it is evident that there is perhaps weak correlation between sensory scores and functional score, but it is far less clear that there is link with global QoL scores. The same is true for motor scores. Table 5.3 details Spearman Rank correlation testing to further explore these relationships.

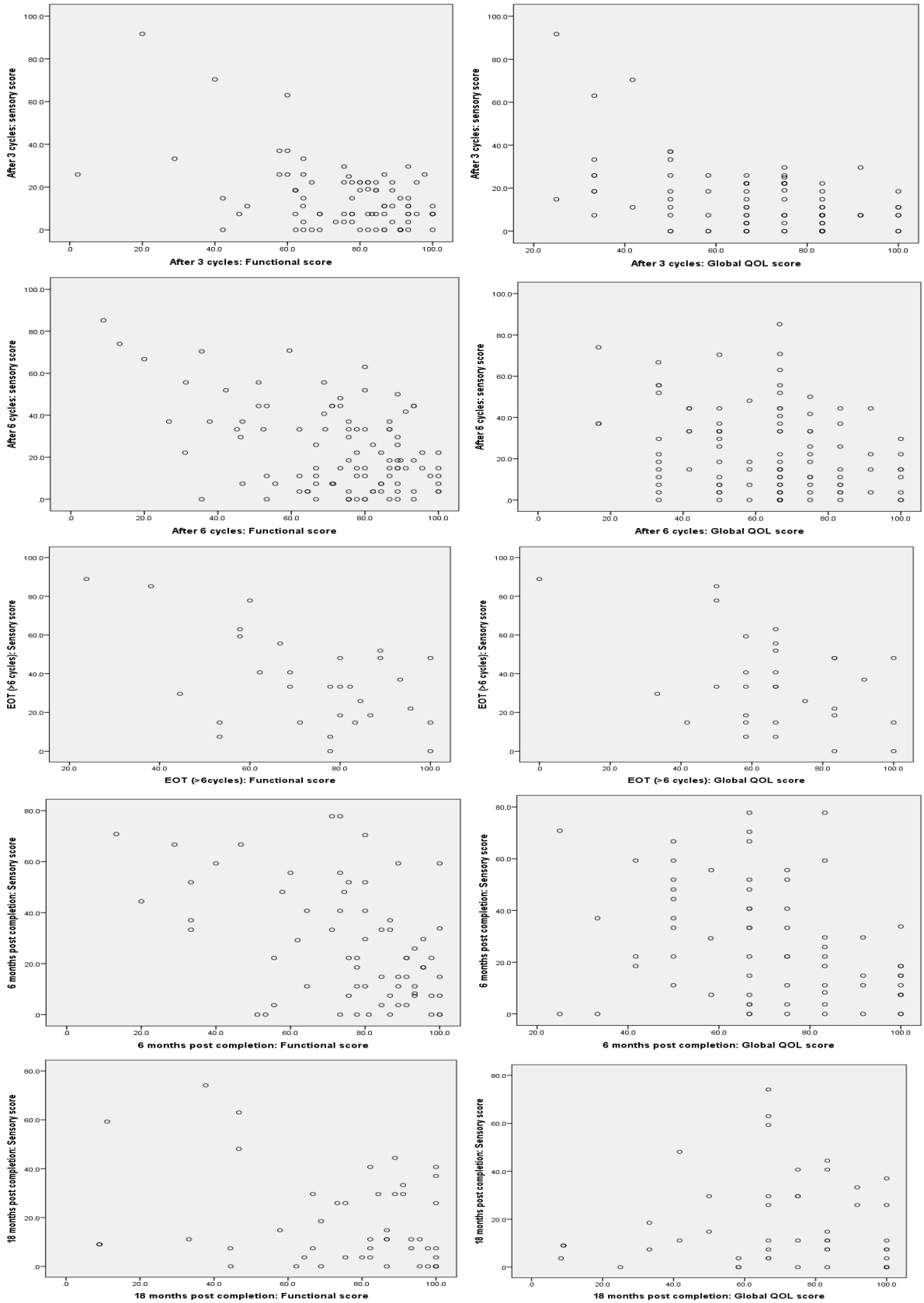


Figure 5.2. Scatter plots of sensory scores against functional scores and global quality of life scores at each time point post-baseline

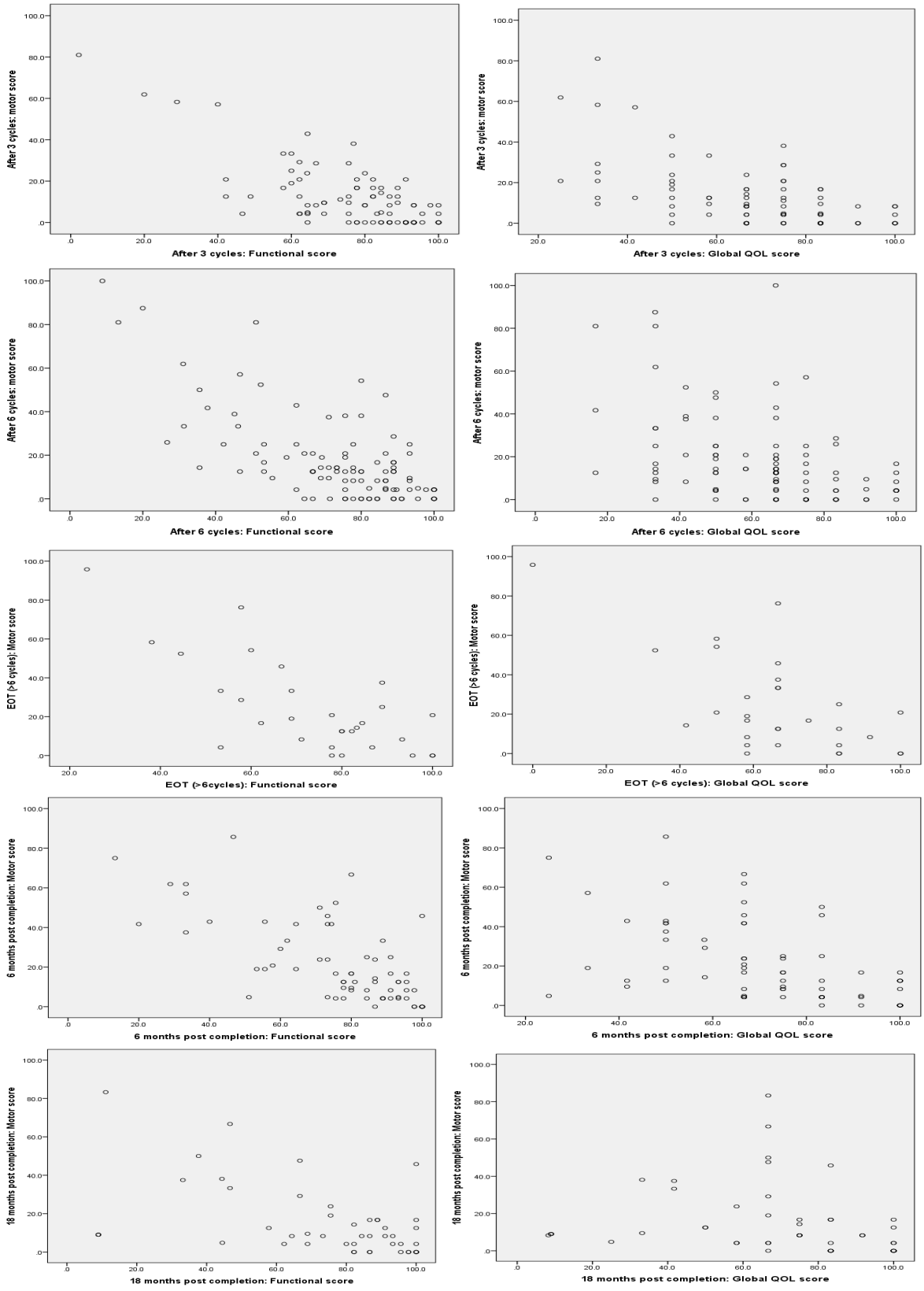


Figure 5.3. Scatter plots of motor score against functional scores and global quality of life scores

Table 5.4. Results of investigation of correlation between sensory and motor scores, respectively and both functional score and global QOL score for the whole cohort

Spearman rank correlation	Baseline	After 3 cycles/ midpoint	After 6 cycles	EOT (if >6 cycles)	6 months	18 months
Correlation between sensory score and functional score	-0.307 **p=0.002** (n=98)	-0.320 **p=0.002** (n=88)	-0.284 **p=0.004** (n=102)	-0.317 p=0.087 (n=30)	-0.396 **p= 0.001** (n=69)	-0.165 p=0.264 (n=48)
Correlation between sensory score and global QOL	-0.226 p=0.025 (n=98)	-0.361 **p=0.001** (n=89)	-0.258 **p=0.009** (n=102)	-0.254 p=0.175 (n=30)	-0.335 **p=0.005** (n=69)	-0.057 p=0.701 (n=48)
Correlation between motor score and functional score	-0.437 **p=0.000** (n=98)	-0.607 **p=0.000** (n=88)	-0.568 **p=0.000** (n=102)	-0.598 **p=0.000** (n=30)	-0.682 **p=0.000** (n=69)	-0.486 **P=0.000** (n=49)
Correlation between motor score and quality of life	-0.422 **p=0.000** (n=98)	-0.582 **p=0.000** (n=89)	-0.465 **p=0.000** (n=102)	-0.504 **p=0.005** (n=30)	-0.580 **p=0.000** (n=69)	-0.447 **p=0.001** (n=49)

It can be seen from the results of Spearman rank correlation analysis that at many time points there was a statistically significant inverse correlation between both sensory scores and motor scores but the correlation was fairly weak. The correlation was actually stronger with motor scores than sensory scores. Reasons for the weak correlation may lie with other factors affecting functional and global QOL scores including a cancer diagnosis, other toxicities from chemotherapy, post-operative recovery in some patients and symptoms related to the underlying cancer which are also likely to have an impact on both of these scores. Sensory scores were correlated with both functional and global QoL scores during chemotherapy and also at 6 months post-chemotherapy. Sensory scores at 18 months follow-up did not correlate with functional and global QOL scores. The numbers are smaller here thereby reducing the power of the study to detect a correlation. Some patients may have then had progressive cancer at this stage and this may impact more strongly on QOL measures than ongoing sensory symptoms or it may be that in the vast majority of patients, sensory symptoms are not predominant enough to cause any impact. Motor neuropathy scores however continue to appear to influence functional and global QOL scores at 18 months post chemotherapy. It may be that those that experience a significant motor element to their neuropathy are those with severe CIPN generally.

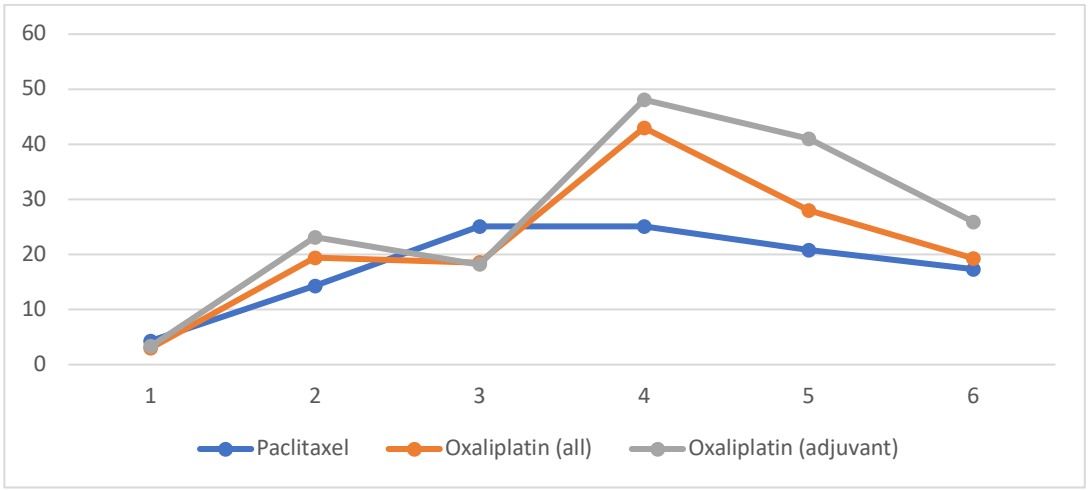
5.3.3 Analysis of the prospective cohorts

For further analysis, the cohort was divided into paclitaxel and oxaliplatin cohorts to identify two groups which were relatively homogeneous with regard to treatment and primary cancer. The paclitaxel prospective group is an all-female population being treated with three weekly schedules of paclitaxel with carboplatin AUC 5 or 6 for ovarian, primary peritoneal or other gynaecological primary.

The oxaliplatin prospective cohort is a group being treated with oxaliplatin with a fluoropyridimine (either intravenous infusion of 5-fluorouracil or oral capecitabine) for colorectal cancer. Of this group, 21 of the 34 patients were being treated adjuvantly post-resection of their primary cancer and 13 were being treated for advanced disease. As seven of the 13 patients being treated for advanced disease were on second or subsequent lines of systemic anti-cancer therapies by completion of the post-chemotherapy follow up time points, exploratory analysis of the adjuvant cohort was also undertaken again to reduce confounding factors.

The tables and graphs below summarise the mean scores for each main category measured on the EORTC-QLQ C30 and for the sensory and motor components of the EORTC CIPN-20.

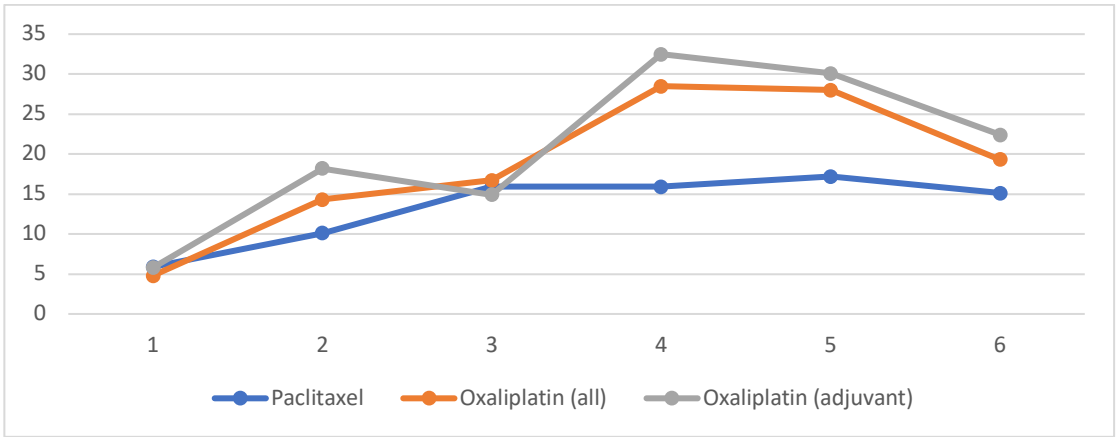
Figure 5.4 shows the sensory scores over time. It can clearly be seen that the mean scores increase rapidly after the start of chemotherapy and continue to increase until the completion of treatment after which time they start to improve. However they remain elevated at a mean of 19.5 at 18 months post-chemotherapy compared with 7.4 at baseline ($p<0.001$, Wilcoxon test). The sensory score remains at the highest level for those who had adjuvant oxaliplatin, presumably due to the higher cumulative dose that these patients would be expected to receive.



Sensory scores	Paclitaxel			Oxaliplatin			Oxaliplatin (adjuvant)		
Time point	n	Mean	SD	N	Mean	SD	n	Mean	SD
Baseline	48	4.3	9.1	34	3.0	5.1	21	3.3	5.8
Mid-point	40	14.3	16.0	25	19.4	17.7	16	23.1	19.4
After 6 cycles	41	25.1	21.6	24	18.5	14.7	14	18.2	14.4
EOT (>6 cycles)				16	43.0	27.3	14	48.1	25.1
6 months	30	20.8	17.6	23	28.0	24.0	16	41.0	27.4
18 months	21	17.3	19.5	18	19.3	19.1	13	25.9	21.7

Figure 5.4 Summary of mean sensory scores for the prospective cohorts

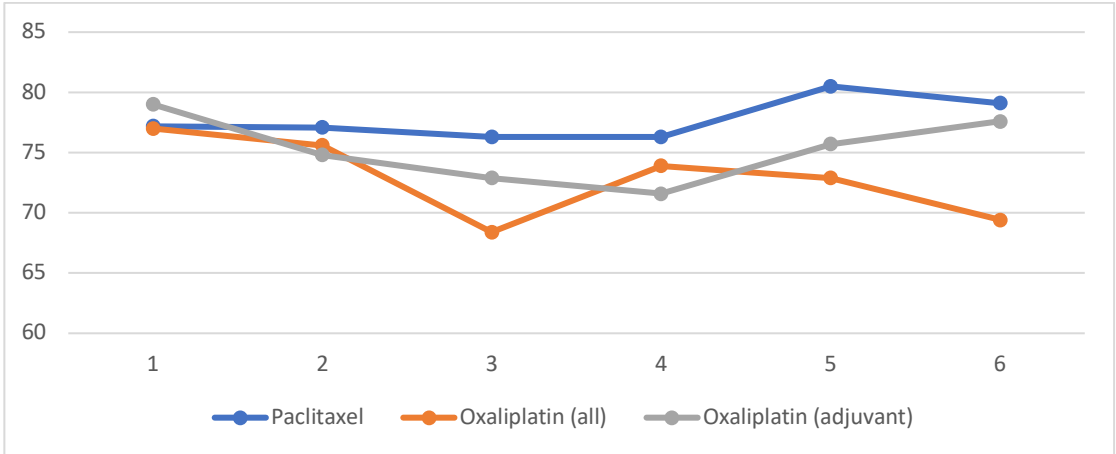
A similar pattern was seen with motor scores (figure 5.5); however whilst the peak motor score was not as high as the sensory scores, as would be expected from these drugs which cause a predominantly sensory neuropathy, the recovery appears less obvious, especially for paclitaxel- treated patients. Motor scores remained an average of 10.2 points higher at 18 months of follow up compared to baseline (9.7 to 19.9, $p < 0.001$, Wilcoxon test).



Motor score	Paclitaxel			Oxaliplatin (all)			Oxaliplatin (adjuvant)		
Time point	n	Mean	SD	n	Mean	SD	n	Mean	SD
Baseline	48	5.9	10.6	34	4.8	9.2	21	5.8	10.4
Mid-point	41	10.1	14.6	25	14.3	14.7	16	18.2	15.8
After 6 cycles	41	15.9	18.0	24	16.7	16.4	14	14.9	12.3
EOT (>6 cycles)				16	28.5	28.9	14	32.5	28.6
6 months	30	17.2	17.3	23	28.0	24.0	16	30.1	27.4
18 months	21	15.1	22.7	18	19.3	19.1	13	22.4	20.6

Figure 5.5. Summary of mean motor scores for the prospective cohort

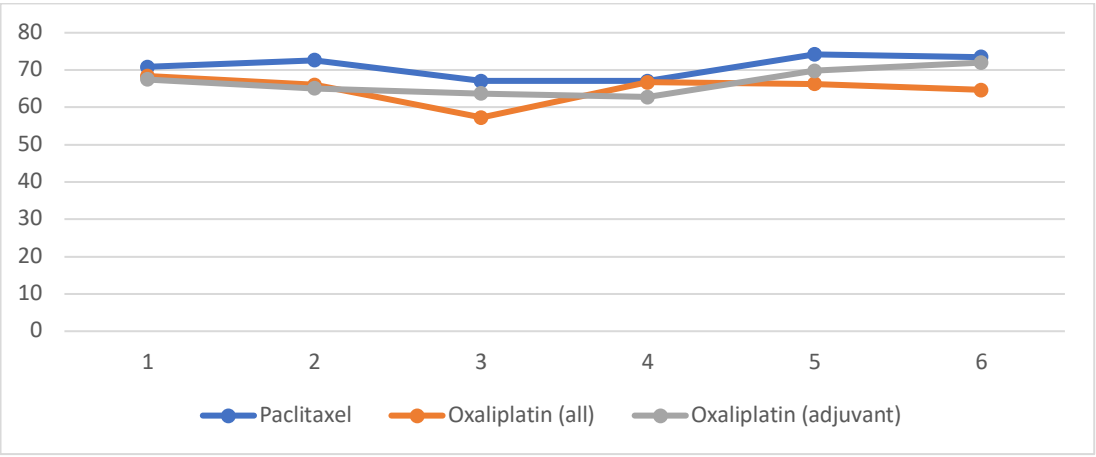
Figure 5.6 summarises the functional scores over time. Functional scores were moderately high throughout with the main dip being towards the end of the course of chemotherapy, particularly in the oxaliplatin- treated patients. Functional scores did not change particularly noticeably for the paclitaxel- treated patients during treatment which may represent symptomatic improvement from their cancer balancing out any chemotherapy toxicity. There was however an increase once chemotherapy was completed. The mean difference between baseline and 18-month scores was not significant (6.3 points, p 0.383).



Functional score	Paclitaxel			Oxaliplatin (all)			Oxaliplatin (adjuvant)		
Time point	n	Mean	SD	n	Mean	SD	n	Mean	SD
Baseline	48	77.2	18.4	34	77.0	24.0	21	79.0	23.8
Mid-point	41	77.1	18.3	25	75.6	15.9	16	74.8	17.1
After 6 cycles	40	76.3	19.3	23	68.4	21.6	14	72.9	23.0
EOT (>6 cycles)				15	73.9	23.0	13	71.6	23.5
6 months	30	80.5	19.8	22	72.9	21.4	16	75.7	21.0
18 months	22	79.1	21.7	16	69.4	34.0	11	77.6	27.0

Figure 5.6 Summary of mean functional scores over time for the prospective group

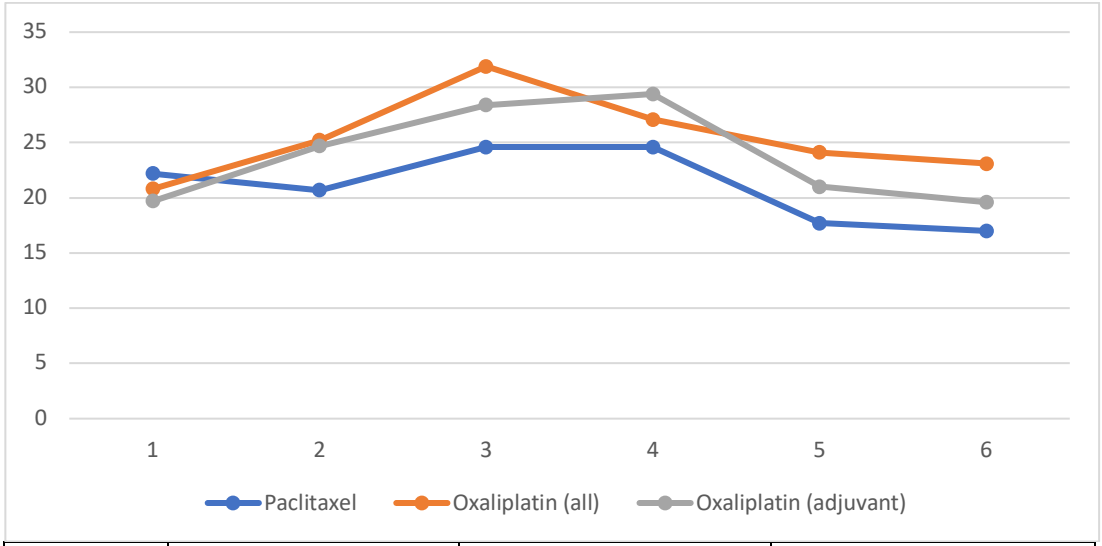
Global quality of life scores are graphically illustrated in figure 5.7. It can be seen that only relatively subtle changes are seen in global quality of life scores over the time course. There is a dip towards the end of chemotherapy but this was only a very small change (mean difference 2.4 between baseline and after 6 cycles of chemotherapy).



Global quality of life	Paclitaxel			Oxaliplatin (all)			Oxaliplatin (adjuvant)		
Time point	n	Mean	SD	N	Mean	SD	N	Mean	SD
Baseline	48	70.8	20.3	34	68.4	24.6	21	67.5	26.6
Mid-point	41	72.6	18.2	25	66.0	17.5	16	65.1	19.5
After 6 cycles	40	67.1	18.4	23	57.3	20.5	14	63.7	21.1
EOT (>6 cycles)				15	66.7	25.8	13	62.8	25.4
6 months	30	74.2	19.1	22	66.3	21.1	16	69.8	19.2
18 months	22	73.5	23.0	16	64.7	32.4	11	72.0	26.2

Figure 5.7 Summary of global quality of life scores for the prospective cohort

Finally, overall symptom scores are summarised in figure 5.8. Again, the peak score was towards the end of chemotherapy but this improved during follow-up, there being no significant difference between baseline scores and 18-month follow up scores (p=0.6).



Symptom score	Paclitaxel			Oxaliplatin (all)			Oxaliplatin (adjuvant)		
Time point	n	Mean	SD	N	Mean	SD	n	Mean	SD
Baseline	48	22.2	16.2	34	20.8	18.5	21	19.7	20.2
Mid-point	41	20.7	15.4	25	25.2	13.8	16	24.7	12.4
After 6 cycles	41	24.6	17.9	24	31.9	18.3	14	28.4	18.9
EOT (>6 cycles)				16	27.1	20.0	14	29.4	20.2
6 months	30	17.7	15.3	22	24.1	18.8	16	21.0	18.0
18 months	22	17.0	15.6	16	23.1	28.0	11	19.6	22.2

Figure 5.8. Summary of overall symptom score over time for the prospective cohort
Correlation between sensory and motor score and functional and global QoL score

The Spearman rank test was used to investigate the correlation between functional and global QoL scores, and each of the sensory and motor scores. Due to the multiple testing, p values of <0.01 were considered significant.

Table 5.5. Results of investigation of correlation between sensory and motor scores, respectively and both functional score and global QOL score for the prospective paclitaxel-treated cohort

Spearman rank correlation	**Baseline**	**After 3 cycles**	**After 6 cycles**	**6 months-post chemotherapy**	**18 months-post chemotherapy**
Sensory and functional	-0.304 p=0.036 (n=48)	-0.291 p=0.068 n=40	-0.043 p=0.793 (n=40)	-0.533 **p=0.002** (n=30)	-0.359 p=0.110 (n=21)
Sensory and QOL	-0.242 p=0.097 (n=48)	-0.349 p=0.027 (n=40)	-0.136 p=0.403 (n=40)	-0.460 p=0.011 (n=30)	-0.212 p= 0356 (n=21)
Motor and functional	-0.508 **p=0.000** (n=48)	-0.546 **p=0.000** (n=41)	-0.447 **p=0.004** (n=40)	-0.831 **p=0.000** (n=30)	-0.562 **p=0.008** (n=21)
Motor and QoL	-0.469 **p=0.001** (n=48)	-0.496 **p=0.001** (n=41)	-0.417 **p=0.007** (n=40)	-0.772 **p=0.000** (n=30)	-0.481 p=0.027 (n=21)

The main finding of note was the significant correlation seen at all time points between motor score and functional score, and at most time points with global QoL in the prospective, paclitaxel-treated cohort. Interestingly, the correlation looked stronger at six and eighteen months post-chemotherapy, which may be due to less confounding factors from other toxicities at these points.

In this smaller cohort, we did not see a statistically significant correlation with sensory scores apart from at the six months post- chemotherapy time point which again suggests that sensory neuropathy is a factor in function post chemotherapy and reaches statistical significance in the absence of other function-influencing toxicities that are likely to be present during the chemotherapy treatment itself.

Table 5.6. Results of investigation of correlation between sensory and motor scores, respectively and both functional score and global QOL score for the prospective oxaliplatin-treated cohort

Spearman rank correlation	**Baseline**	**After 3 cycles**	**After 6 cycles**	**End of treatment (if >6 cycles)**	**6 months-post chemo**	**18 months-post chemo**
Sensory score and functional score	-0.482 **p=0.004** (n=34)	-0.368 p=0.071 (n=25)	-0.509 p=0.013 (n=23)	-0.733 **p=0.002** (n=15)	-0.11 p=0.622 (n=22)	-0.234 p=0.383 (n=16)
Sensory score and global QOL	-0.314 p=0.071 (n=34)	-0.451 p=0.024 (n=25)	-0.331 p=0.123 (n=23)	-0.729 **p=0.002** (n=15)	-0.086 p=0.704 (n=22)	-0.207 p=0.442 (n=16)
Motor score and functional score	0.516 **p=0.002** (n=34)	-0.649 **p=0.000** (n=25)	-0.733 **p=0.000** (n=23)	-0.748 **p=0.001** (n=15)	-0.483 p=0.023 (n=22)	-0.447 p=0.082 (n=16)
Motor score and global QoL	-0.385 p=0.025 (n=34)	-0.567 **p=0.003** (n=25)	-0.392 p=0.065 (n=23)	-0.730 **p=0.002** (n=15)	-0.334 p=0.128 (n=22)	-0.444 p=0.085 (n=16)

In the oxaliplatin-treated prospective cohort, once again, the strongest correlation was between motor score and functional score, although in this group, it did not quite meet statistical significance at the post-chemotherapy time points. Crucially the number of patients in this cohort was smaller and therefore the power to detect such differences was smaller. From the graph of motor score over time, there appeared to be greater improvement in motor scores in the oxaliplatin group than in the paclitaxel group which may also have contributed to the lack of significance. There was also more confounding in

this group due to the fact that more patients in the oxaliplatin cohort as compared with the paclitaxel cohort had started second line chemotherapy at the 6 and 18 month time points which is likely to have its own impact on both functional score and QoL. In terms of the sensory score, the only time point at which there was correlation between functional score or global QoL score was at the end of the treatment point for those patients who received more than six cycles of chemotherapy.

5.3.4 Persistent CIPN, functional score and quality of life

Sub-group analysis restricted to those patients with persistent neuropathy at 18 months post chemotherapy was as an exploratory analysis because of the limited sample size. The mean baseline sensory score was 7.4. As stated above, using evidence that a ten point difference in many symptom based scores in cancer-related QOL scales is often considered the lower estimate of a clinically meaningful effect (408, 409), a cut-off of 17.4 was used to arbitrarily define those with persistent sensory neuropathy and those without. Similarly, recognising that 9.7 was the mean baseline motor score, a cut-off of 19.7 was used to define persistent motor neuropathy. By these definitions, 15 patients had persistent sensory neuropathy (8 paclitaxel-treated patients and 7 oxaliplatin- treated patients) and 8 had persistent motor neuropathy (3 paclitaxel-treated patients and 5 oxaliplatin-treated individuals). There was no statistically significant difference between global QOL and functional scores for those either with or without persistent sensory neuropathy within the prospective cohort. However, again motor neuropathy seemed to be more problematic with a statistically significant difference in the functional score ($p=0.002$) and global QOL score ($p=0.026$) at the 18 month time point.

5.3.5 Analysis of CIPN-20 scores and NCI CTC grading of CIPN

Figure 5.9 shows the mean sensory scores illustrated over the time period of the study based on groups of patients defined by the maximum recorded NCI CTC grade (0-3) during chemotherapy. There was a significant difference in mean sensory scores at the post- 3 cycles, post- 6 cycles, end of treatment (where >6 cycles) and 6 month post-chemotherapy time points. This was not statistically significant at the 18 month time point but the difference in mean scores for those assessed as experiencing grade 3 neuropathy during

chemotherapy appeared to be notably higher than those with grade 0-2 sensory neuropathy during treatment. This would appear to support the clinician grading within this study group and replicate the correlation that has been previously noted between NCI CTC grading and the CIPN-20 sensory score.

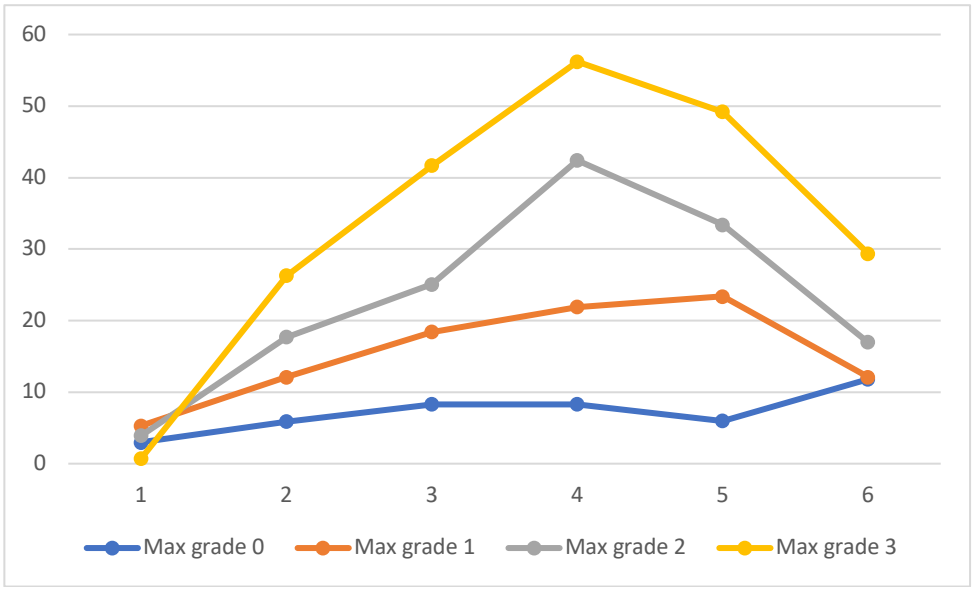


Figure 5.9. A graph to show sensory score over time according to NCI CTC grade.

Figures 5.10 and 5.11 show functional and global QoL scores over the time points for the four different maximum NCI CTC grading categories, respectively. There was no clear relationship with quality of life and a significant relationship with functional score was demonstrated only at the post- cycle 6 time point (p=0.001).

Contrasting this with the results seen with the CIPN20 scores, this suggests, as may be expected, that the CIPN20 is far more responsive to differences in severity of symptoms within the broad grade categories of the NCI CTC grading scale.

Max grade (NCI CTC)	Mean sensory score					
	Baseline	Midpoint	After 6 cycles	EOT (<6 cycles)	6 months	18 months
0	3.006	5.876	8.3	59.3 (1)*	6.0	11.8
1	5.3	12.1	18.4	21.9	23.4	12.1
2	3.9	17.7	25.1	42.4	33.4	17.0
3	0.7	26.3	41.7	56.2	49.2	29.4
Anova test p value	p=0.344	p=0.001	p=0.000	p=0.007	p=0.000	p=0.084

*Spurious result, omitted for purposes of graphing but not analysis.

Table 5.7 Table detailing mean sensory scores per maximum NCI CTC grading category and ANOVA test results

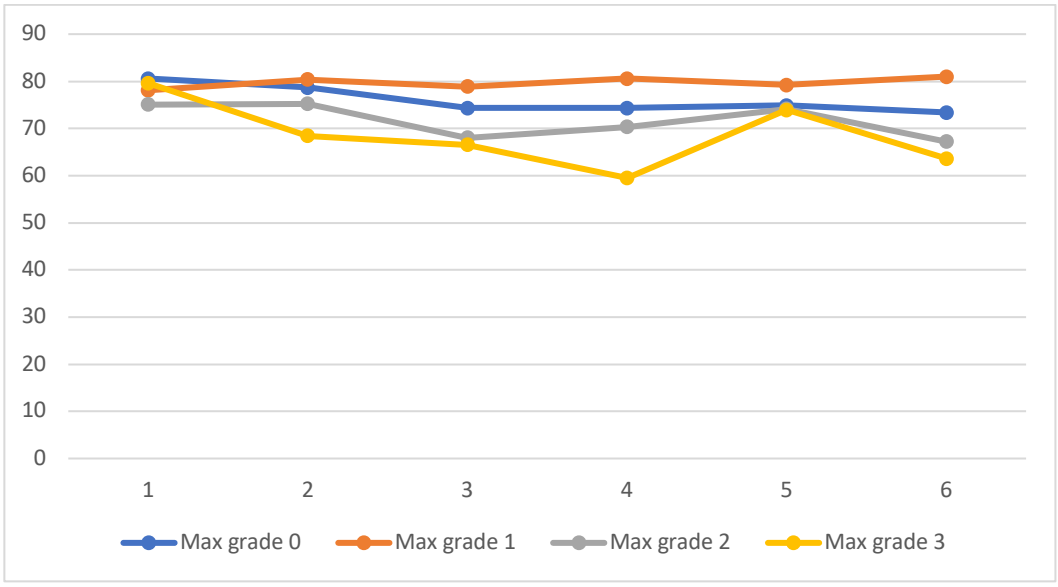


Figure 5.10. A graph showing mean functional score over time categorised according to maximum NCI CTC sensory neuropathy grading

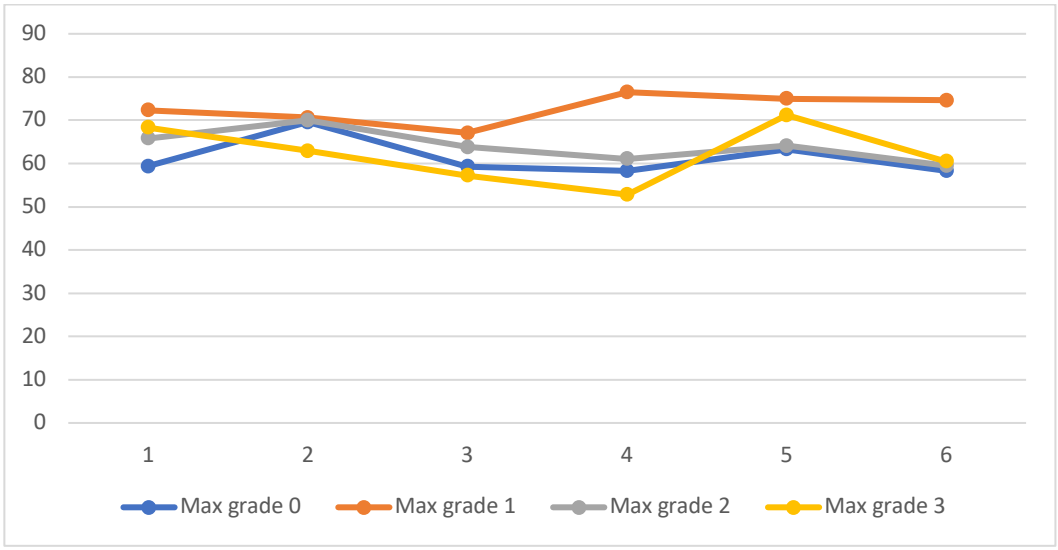


Figure 5.11 A graph showing mean global QoL score over time categorised according to maximum NCI CTC sensory neuropathy grading

5.4 DISCUSSION

This study demonstrates a significant inverse correlation between sensory and motor scores on the CIPN20 with functional and global QoL scores on the EORTC-QLQ-C30 at most timepoints for the cohort as a whole. The correlation is not strong but it is clearly present. It is perhaps unsurprising that there is not a stronger correlation due to the multiple other

symptomatic, social, psychological and cancer-related factors that may be also impacting on function and overall QoL during and in the months following chemotherapy. In the separate paclitaxel- and oxaliplatin- treated prospective cohorts, there was some correlation but it was only statistically significant at a small number of time points. In the paclitaxel cohort, the sensory score was negatively correlated with functional score at 6 months post-chemotherapy, probably because other chemotherapy-related side effects had subsided and neuropathy potentially had a greater influence on function. Motor scores, however, were negatively correlated with functional and global QoL scores at all except one time point. The 18 month post-chemotherapy time point showed a trend probably because of limited sample size. In the oxaliplatin cohort, at the end of treatment time point for those patients receiving >6 cycles, there was a significant negative correlation between the sensory score and both functional and global QoL scores.

The general trend for all results was a more significant correlation with motor score as compared with the sensory score. This is perhaps surprising in a predominantly sensory neuropathy. There may be a number of reasons for this: it may simply be that when motor neuropathy occurs it results in more significant impact on normal functioning. It could also be argued that those with motor symptoms have more severe levels of neuropathy. It could also be related to the questionnaire and how motor and sensory score were separated and the questionnaire items used to build each score.

Whilst the EORTC CIPN-20 is clearly a well-validated and meaningful tool to collect patient-reported data regarding CIPN, like many patient report modules, it does have its potential problems and the categorisation of items in the module into ‘sensory’ and ‘motor’ is not completely clear cut, particularly for certain questions. For example, the question regarding presence of difficulty standing up due to weakness in your legs could answered ‘very much’ difficulty when the predominant symptom is fatigue. ‘Motor’ items such as difficulty holding a pen or manipulating small objects in your fingers could equally indicate sensory neuropathy impairing the ability to appreciate the objects between your fingers rather than a motor neuropathy being responsible. It may be that high scores on certain ‘motor’ items are not purely assessing motor neuropathy, but are inadvertently representing marked sensory impairment. The question regarding hearing as a sensory item could be argued as being unhelpful unless being used for potentially ototoxic drugs such as cisplatin.

Confounding is the main limitation of this study. Whilst prospective drug-specific, tumour-specific groups were examined separately as well as together, other confounding factors such as stage of cancer, surgical management and other co-morbidities were not taken into consideration in this study leading to heterogeneity within the study population. Similarly, there was no control for other chemotherapy-related toxicities which may also cause functional effects particularly during the chemotherapy period.

A further limitation of the study is that because the time points for quality of life assessment were driven by cycle numbers, those that stopped chemotherapy early due to neuropathy were missing from the end of treatment assessments as their 'end of treatment' may have been, after for example, only 6 cycles, whereas they may have been planned to have 8 or 12 cycles. There are also a number of patients who were receiving second line chemotherapy regimens at the post-treatment, follow up time points which may have affected scores. Sample size in the later time points was small which reduced the power of the study; however the starting sample sizes were comparable, and in some cases, better than previous CIPN-related quality of life studies.

Missing data is frequently an issue in longitudinal quality of life studies in cancer (410). Some of this is unavoidable due to the nature of the disease causing deterioration in health, death or a wish of patients to put their cancer behind them and not be reminded of it by completing forms related to chemotherapy after the treatment course is finished. However, the amount of missing data could have perhaps been improved with more study support and using the limited support available more effectively. I was relying largely on seeing the patients personally at the designated time points during chemotherapy. However, with hindsight and in different circumstances I would have utilised the small amount of data support I had to help chase these up and perhaps given the patients the assessment forms upfront and used telephone prompts to remind patients to return them in pre-paid envelopes in case I was not able to review the patients in person on the correct day.

One of the most important findings of this study is the finding that those with persistent 'motor' neuropathy symptoms as assessed by the CIPN-20 module have persistently significantly lower functional scores. This is notwithstanding the small sample sizes at this point. This reinforces the importance of this side effect and the need to continue to build

our understanding of the factors that predispose an individual, and understand mechanism, so that this may eventually lead to preventative strategies.

5.5 CONCLUSION

This chapter has highlighted the effects of CIPN on quality of life. The study demonstrates that there can be persistence of significantly elevated levels of CIPN20 sensory and motor scores 18 months after completion of taxane and oxaliplatin-based chemotherapy. The main finding of note is that whilst CIPN is generally recognised as a predominantly sensory neuropathy, it is the motor score on the CIPN20 which seems to produce more functional and quality of life impairment, and this is shown to be persistent even 18-months after completion of chemotherapy.

CHAPTER 6

DISCUSSION AND FUTURE DIRECTIONS

This collection of work has systematically assessed the clinical and genetic risk factors that may lead to the development of CIPN. I have described how drug, cumulative dose, duration of infusion and possibly scheduling may have an impact on the risk of neuropathy. Body mass index warrants further investigation as a risk factor for the development of this adverse effect and the racial differences observed in toxicity, particularly with regard to vincristine need to be further explored. Beyond this, there is currently little to define the at-risk individual for CIPN.

Chapter 2 described the multiple studies previously performed with the aim of identifying genetic risk factors. It highlighted the need to be robust with respect to phenotypic definition and echoes others working in CIPN research in calling for consensus on outcome measures (138).

The candidate gene study was not able to confirm associations in the selected putative SNPs. The small study size was the main limitation and phenotypic characterisation the biggest strength. This was the first study to attempt replication of association of taxane induced peripheral neuropathy and *CYP3A4*22,* and in fact showed no association within this cohort with a greater number of 'cases' and may therefore be argued to be more likely to be a true reflection of the influence or otherwise of this variant in development of CIPN. The GWAS-identified variants selected for investigation in relation to taxane induced neuropathy again were not replicated in this cohort and this is in agreement with a recent study also looking to replicate these findings in a UK population (274). For oxaliplatin induced peripheral neuropathy, variants identified in Asian GWAS and candidate studies (94, 272) as possibly being associated with development of cumulative oxaliplatin induced neuropathy were similarly not replicated in this project.
The SNPs were chosen at a time point dictated by the point in progress through the project. Since then, other studies (89, 274, 344) have agreed with conclusions of this study in relation to the SNPs genotyped, while other studies have identified other variants (321, 322). Building of a biobank of well-defined case and control subjects with patient reported outcome data to support categorisation has the potential to be an asset to continue to explore further potential associations. In the field of taxane induced peripheral neuropathy the Charcot Marie Tooth related genes, in particular *ARGEF10*, (321, 322) warrant further

investigation, as do variants in *TUBB2A* (274). In the case of oxaliplatin induced peripheral neuropathy, GWAS in a large Causcasian population with well-defined phenotypic categorisation is warranted as it is difficult to identify SNPs from the current literature that warrant further investigation.

A strength of the study was to use both patient reported outcomes alongside a standard grading tool such as the NCI CTC grading score. Although the optimal study outcome measures with regard to CIPN are yet to be agreed, it could be argued that clinical assessment of CIPN could have been improved upon by using the Total Neuropathy Score (clinical) rather than using NCI CTC grading. This was considered but was not believed to be feasible due to practical constraints within the study. Due to the limited funding there was always going to be a very limited number of trial professionals involved in the assessment of patients and a more involved assessment of neuropathy would have created barriers of both time and space for such examinations and may have impacted on recruitment. There was also a training issue as the study was rolled out to multiple centres. Research practitioners would have to be trained in testing of deep tendon reflexes and vibration testing as inaccuracies in performing this test can result in greater inconsistency between grading. For a more complete assessment of CIPN however a visual analogue scale could have been added for neuropathic pain which was not well accounted for in assessment of the patients in this study. It was recorded wherever possible in the quality of life study cohort but I suspect this was an underestimate of the true incidence in this population. From the quality of life investigation, it was demonstrated that both sensory and motor scores remained clinically and statistically significantly elevated at 18 months post chemotherapy completion. Relatively weak negative correlation was seen between sensory score and motor score and quality of life and functional scores, respectively at most time points. The weak correlation could be due to the many other confounding factors that may exist for each individual going through a course of chemotherapy for cancer including other toxicities and cancer symptoms, and emotional wellbeing. The correlation was stronger for motor neuropathy and indeed persistent motor neuropathy was significantly associated with poorer functional and global QOL status than those without persistent motor neuropathy, whereas this was not the case for sensory neuropathy. This indicates that motor neuropathy symptoms are more detrimental to normal activity; however it may also

be a function of the CIPN20 since some of the items on the motor score may also be attributed to marked sensory neuropathy or fatigue. As always, experience in research is a learning curve. If I were to repeat the project I would aim to develop more robust methods of collecting follow up quality of life assessments. Missing forms is frequently an issue in longitudinal quality of life studies in cancer (410) due to a multitude of reasons previously mentioned; however providing patients with the questionnaires upfront at recruitment with return envelopes and using telephone prompts may have improved return rates.
For both the pharmacogenetics and quality of life studies, ideally greater numbers should have been included. Within the time constraints of the project and limited research staff to support recruitment and follow up, this was the maximum that could be achieved. Recruitment continues however through the NIHR portfolio Molecular Genetics of Adverse Drug Reactions study and future analyses will therefore have greater power to detect potentially small but significant effects, particularly when looking at the complex genetic variants which may be hypothesized to contribute to an 'at-risk' genotype.

This thesis has comprehensively explored clinical and genetic risk factors for development of CIPN. It has added to the evidence regarding pharmacogenetics risk factors and supports evidence of a statistically significant link to reduced quality of life with CIPN both during, but more importantly after chemotherapy.
Oncological management of malignancy frequently involves weighing up potential benefits of toxic treatments against their potential adverse effects. The adverse reactions and size of benefit varies between different treatment schedules in different cancers. The ideal scenario would be one where instead of weighing up general median benefits and side effects, it was possible to personalise these discussions to individual patients. This would be particularly important in situations where the benefit of a specific treatment is modest but the risk of long term adverse reactions is significant. Whilst countless studies are performed for assessing the efficacy of new drugs with translational aspects focusing on biomarkers of response, very few studies focus on toxicity, and impact on survivorship. This situation needs to be improved, as it is only through studies that are specifically set up and designed to investigate and characterise the 'at risk' phenotype and genotypes, that we will truly achieve individualised care that takes into account cancer survivorship and long term quality of life.

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APPENDIX

A Study to Investigate the Incidence, Impact on Quality of Life and Pharmacogenetics of Chemotherapy Induced Peripheral Neuropathy.

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Funders

Clatterbridge Centre for Oncology Charitable Trust
Clatterbridge Cancer Research Trust
In collaboration with the University of Liverpool, Department of Pharmacology and Therapeutics

This protocol describes the CIPN study and provides information about procedures for entering participants. Every care was taken in its drafting, but corrections or amendments may be necessary. These will be circulated to investigators in the study..
Problems relating to this study should be referred, in the first instance, to the Chief Investigator.

This study will adhere to the principles outlined in the NHS Research Governance Framework for Health and Social Care (2nd edition). It will be conducted in compliance with the protocol, the Data Protection Act and other regulatory requirements as appropriate.

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GLOSSARY OF ABBREVIATIONS

CIPN	Chemotherapy induced peripheral neuropathy
QOL	Quality of Life
EORTC	European Organisation for Research and Treatment of Cancer
NCI CTC	National Cancer Institute Common Toxicity Criteria
CCO	Clatterbridge Centre for Oncology
DNA	Deoxyribose nucleic acid
SNP	Single nucleotide polymorphism
CNV	Copy number variant
MAP	Minor allele frequency

KEYWORDS
Chemotherapy- induced peripheral neuropathy, Pharmacogenetics

STUDY SUMMARY

TITLE ***A Study to Investigate the Incidence, Impact on Quality of Life and Pharmacogenetics of Chemotherapy Induced Peripheral Neuropathy in Patients Treated with Taxane and Oxaliplatin Chemotherapy.***

POPULATION *Patients who have received, or are due to commence chemotherapy regimens containing 3 weekly docetaxel or paclitaxel, or 2 weekly oxaliplatin either as single agents or in combination with other drugs will be eligible for entry into the study. Patients who have received these drugs within the preceding 18 months or are due to commence these agents will be eligible.*

PRIMARY AIMS *To determine the incidence, persistence and impact on quality of life of chemotherapy induced peripheral neuropathy*

SECONDARY AIMS *To investigate for molecular genetic risk factors predisposing to development of chemotherapy induced peripheral neuropathy (CIPN) and through this investigate the possibility of genetic tests which can help in predicting individual susceptibility to CIPN and gain a better understanding of the mechanisms in development of CIPN.*

ELIGIBILITY

Age 18 and above with no exclusion criteria

Receiving either oxaliplatin or 3 weekly taxane containing chemotherapy regimen for the prospectively recruited population of the study

OR

Received either oxaliplatin or a 3 weekly taxane containing chemotherapy regimen within the last 18 months for the retrospectively recruited population of the study

No pre-existing peripheral neuropathy

No subsequent treatment with oxaliplatin, taxanes, cisplatin or vinca alkaloids since the index course of chemotherapy

1. INTRODUCTION

1.1 BACKGROUND

Advances in oncology mean that patients are living longer with a cancer diagnosis following treatment. As a consequence survivorship issues are becoming increasingly important and there is a definite need to consider the long term side effects of cancer treatment. Chemotherapy induced peripheral neuropathy (CIPN) is a common side effect during treatment and for a significant number of patients it can persist for a long period of time following completion of treatment with significant impact on function and quality of life (QOL). Neurotoxicity is a common reason leading to dose reduction or early cessation of chemotherapy.

The mechanism of CIPN is poorly understood but there is emerging evidence that susceptibility to drug induced neurotoxicity can be predicted by an individuals' genotype.

The proposed study aims to establish the incidence of CIPN in patients treated with taxane and oxaliplatin chemotherapy and its impact on QOL. It will also aim to determine whether certain genetic polymorphisms confer susceptibility to CIPN in order to identify a mechanism to predict which patients are at risk of long term neurotoxicity. If certain polymorphisms do confer susceptibility, as is suspected, it may guide therapeutic strategies and potentially aid development of concurrent neuroprotective therapy during chemotherapy.

1.2 RATIONALE FOR CURRENT STUDY

Taxane induced peripheral neuropathy can affect up to 50-60% of patients with up to 33% of patients experiencing more severe neuropathy (NCI CTC grade 3-4) [1]. Oxaliplatin neurotoxicity has two distinct manifestations: acute, transient symptoms are due to peripheral sensory and motor neurone hypersensitivity and occur in up to 90% of patients [2]; cumulative more chronic peripheral neuropathy that interferes with function occurs in 15-20 of patients [3,4]. The cause of the acute neuropathy is believed to be due to a channelopathy (a temporary dysfunction of an ion channel in the nerve membrane), while chronic sensory neuropathy may be a result of direct, cumulative neurotoxic effects resulting from platinum accumulation in the dorsal root ganglion[5,6]. The mechanism is poorly understood, however, and other pathways have been proposed [7].

Estimates of the proportion of people affected by persistent neuropathy within clinical trials are made in the literature supporting these drugs' efficacy and defining use in current practice. In clinical practice however these rates are suspected to be somewhat higher and little work has been done on the impact on quality of life. In addition, it has been shown that some chemotherapy toxicities can be underestimated by medical staff [8]. In recent years an EORTC module, CIPN-20, has been developed to aim to gain better information on CIPN- related symptoms and the impact of function [9]. This questionnaire is currently in phase IV of development and we will use this along with the QLQ C30 to

investigate patients' experience. A better understanding of these effects along with possible predictive factors of those patients most susceptible to this adverse effect through the identification of biological markers would allow more rational treatment decisions regarding taxane and oxaliplatin use.

Recent data has identified a link between genetic variants of TMPT and COMT genes and the development of hearing- related toxicity in children receiving cisplatin chemotherapy [10] and a similar pharmacogenetic susceptibility or resistance has been speculated to exist in the case of taxanes and oxaliplatin and neurotoxicity.

In the case of peripheral neuropathy there has been interest in Wlds (slow Wallerian degeneration gene) and CYP3A genotypes. It was noted that mice with a spontaneous mutation in the Wlds gene displayed delayed axonal degeneration after transection of nerves. To investigate this phenomenon further the gene was transferred to rat neurones and they were exposed to vincristine. Neurones containing the mutant Wlds protein were resistant to vincristine neuropathy whereas those with the wild type protein product underwent degeneration [11]. A similar study exposed both wild type and Wlds mutant mice to paclitaxel and again was able to show that Wlds mice were resistant to neurotoxicity [12].

A more recent publication reported a correlation between patients with certain GSTP1 polymorphisms and the development of NCI CTC grade 2 or greater peripheral neuropathy with docetaxel treatment [13]. GSTP1 polymorphisms have also been linked to a susceptibility to cumulative oxaliplatin neurotoxicity. In one study exploring this association it was found that those patients with Ile/Ile GSTP1 exon 5 genotype were significantly more likely to experience NCI CTC grade 3 cumulative neurotoxicity and those homozygous or heterozygous for the GSTP1 105Val allele had a lower risk[14]. This finding has been reproduced in 71 patients receiving oxaliplatin and 63 patients receiving cisplatin [15]. Other putative pharmacogenetic markers have been explored based on theories of mechanisms of neurotoxicity and metabolism of the drug. Associations have been proposed with TS and MTHFR [16], as well as AGXT minor haplotype [7], a marker of the functioning of the oxalate outcome pathway, and oxaliplatin neurotoxicity.

It is envisaged that through increasing exploration of putative predictive pharmacogenetic factors a more thorough understanding of the mechanisms of development of CIPN may be achieved, along with a mechanism of identifying patients who will be more susceptible to these potentially long- lasting side effects to better inform decisions about treatment selection to aim for more individualised therapy.

2. STUDY OBJECTIVES

The primary objective is to determine incidence and persistance of NCI CTC (version 3.0) grade 2 or greater neurotoxicity in patients treated with 3 weekly taxane or oxaliplatin containing regimens in routine clinical practice with assessment of quality of life related to CIPN using EORTC QLQ C30 score and EORTC CIPN-20 score.

The second objective is to analyze blood samples for potential pharmacogenetic biomarkers which may be associated with an increased risk of developing CIPN. Through this investigation the aims are to identify possible genetic risk factors which may predispose to CIPN and gain an increased understanding of the mechanisms involved in its development.

3. STUDY DESIGN

There will be two strands to the project; a retrospectively recruited sample of patients and a prospectively recruited sample of patients.

A retrospective group will be identified by using the hospital computer system to generate a list of patients who have undergone a course of oxaliplatin- containing chemotherapy or a 3 weekly taxane based regimen, completing treatment within the last 18 months.

These patients will be invited to participate either at a routine follow up appointment where interested patients will be given a patient information sheet, or by post with a standard letter explaining the study, its purpose and why they are being invited to participate. It will also include the patient information leaflet. There will be 2 options for contacting us to express interest in participation 1) return by post of a form 2) the phone number for the research nurse to express interest.

When patients have expressed interest they will be given an opportunity to further discuss the study and have their questions addressed in clinic where their eligibilty will be confirmed and if they are still keen to participate they will be asked to sign a written consent form. The research nurse will complete a case record form (CRF). Representative data to be collected will include the details of the patients chemotherapy regimen, and any subsequent chemotherapy, total cumulative dose of the taxane/ oxaliplatin, the patients age, height, weight, ethnicity, their primary diagnosis and any relevant co-morbidities or risk factors for peripheral neuropathy as well as any concomitant medication (***Appendix***.

The research practitioner will take a record of any symptoms of peripheral neuropathy experienced during chemotherapy and following chemotherapy and will make an assessment of any current peripheral neuropathy symptoms. This will be done from the casenotes and from patient report. The patient will then be asked to complete an EORTC QLQ C30 and an EORTC CIPN 20 form. All paperwork will be labelled with a patient code number so that no patient identifiable data is attached to the forms. For the pharmacogenetic component of the study one 9ml blood sample will be taken in a standard EDTA collection tube by an appropriately trained health care professional. Once these activities have been completed the patients' involvement in the project is complete. The information collected will be used to define the patient as a 'case' or as a 'control'. 'Cases' will meet criteria for having NCI CTC (version 3.0) grade 2 sensory, motor or combined peripheral neuropathy. 'Controls' will have no history of anything greater than grade 1 cumulative peripheral neuropathy.

The prospectively recruited patients will be patients commencing a course of treatment with taxane-based or oxaliplatin containing chemotherapy. They will be identified through their treating medical

team or by clinical members of the research team. Medical staff routinely treating patients with these agents will be made aware of the project through notices sent by email and circulated with current research updates throughout Clatterbridge Centre for Oncology. Patients will be informed of the study once their course of treatment has been planned and if the patient is interested a patient information leaflet will be given to them to read. Once they have had an opportunity to read and digest the information they will be asked for their opinion about participation with an opportunity for questions and further discussion, and if they would like to participate, written consent will be obtained. The same data set will be completed and coded and the EORTC QLQ C30 and CIPN 20 will be completed. During chemotherapy, patients will be asked to complete the EORTC QLQ C30 and CIPN 20 questionnaires after 3 cycles of chemotherapy and then after 6 cycles of chemotherapy. If the patient is proceeding to more than 6 cycles of chemotherapy then they will be asked to complete the questionnaires at the end of chemotherapy. After completion of chemotherapy they will be asked to complete further questionnaires at 6 months post chemotherapy and at 18 months post completion of chemotherapy. Data will be collected throughout chemotherapy regarding any dose reductions or regimen modifications for peripheral neuropathy. For the pharmacogenetic component of the study each participant will have one blood sample taken by an appropriately trained health care professional. A 9ml blood sample will be collected in an EDTA blood collection bottle from each patient. The information gained from clinic review and patients self- report questionnaires will be used to define patients as 'cases' if they meet the criteria for NCI CTC grade 2 or greater sensory, motor or combined peripheral neuropathy developing during or within 4 weeks after chemotherapy, and 'controls' if there is no evidence of peripheral neuropathy or if there has been transient grade 1 peripheral neuropathy only during or after chemotherapy.

Handling, testing and storage of blood samples

Once the blood sample has been collected it will be labelled with the same patient code as their questionnaires and study related clinical data to ensure no patient identifiable information is transferred. The sample will be packaged in a Royal Mail approved blood sample pack and sent to the University of Liverpool, Department of Pharmacology Laboratories where the samples will be processed, DNA extracted and stored securely in a locked freezer. All biological samples stored within the Department of Pharmacology Laboratories are in keeping with the Human Tissue Act.
For initial analysis candidate susceptibility genes will may include GSTP1, AGXT, ERCC1, TS, MTHFR, C118T, GSTM and Wids. However clearly initial analyses and further updated information may generate further putative genes and further analyses would be performed based on these.
We will analyse for associations with genetic polymorphisms using statistical support at the Wolfson Institute for Personalised Medicine, University of Liverpool.
The samples will not be used for any other genotypic analysis for any other conditions without the further permission of the Ethics Committee. After all the clinical data has been collected, the coded

samples will be completely anonymised, and will not be traceable to any individual subject. Genotypic data will be kept by the Department of Pharmacology & Therapeutics at the University of Liverpool (under secure conditions). Participants and/or their GP's will not be told of the genotypes identified from the studies at any stage during the study. Neither will this information be routinely disclosed to any third party in any event. In addition, as the samples are anonymised, and the study is investigating a complex genetic trait, the results will not affect the ability of the patients or their families to obtain insurance.

4. PARTICIPANT ENTRY

4.1 PRE-REGISTRATION EVALUATIONS

Assessment of eligibility will be evaluated from clinical data held on clinical databases and patient notes.

4.2 INCLUSION CRITERIA

Patients must be 18 years old or over

and are receiving either oxaliplatin or 3 weekly taxane containing chemotherapy regimen for the prospectively recruited population of the study

or who have received either oxaliplatin or a 3 weekly taxane containing chemotherapy regimen within the last 18 months for the retrospectively recruited population of the study

Willing to take part and sign a consent form

4.3 EXCLUSION CRITERIA

a) Does not meet inclusion criteria
b) Pre- existing peripheral neuropathy prior to chemotherapy.
c) Subsequent treatment with cisplatin or a vinca alkaloid since completion of treatment with a taxane or oxaliplatin, or a second course of taxane or oxaliplatin within the study period

4.4 WITHDRAWAL CRITERIA

As there is no investigational product or change in routine management there are no pre-set stopping criteria however patients can choose to withdraw from the study at any time during their involvement. Once all data has been collected and clinical correlation with pharmacogenetic analysis made the blood samples the codes linking the sample to individual patients will be removed so making the samples not traceable to an individual patient. Once this has occurred, which would be after the active involvement of the patient, the patient would not be able to withdraw their sample.

5. ADVERSE EVENTS

The study involves no investigational product or significant change in routine clinical management and therefore the likelihood of adverse events is small. Venepuncture can cause some brief discomfort and can be associated with minor bruising. Any discomfort will be minimised by ensuring appropriately trained health care professionals perform sample collection and where this can be done at the same venepuncture as blood sampling for routine checks this will occur.

6. ASSESSMENT AND FOLLOW-UP

For retrospectively recruited patients their involvement in the study will end as soon as their study related data is recorded, the EORTC QLQ C30 and CIPN 20 forms are complete and the blood sample taken. It is envisaged that this will occur in a single visit. They will continue with routine clinical follow up with their usual medical team.

For prospectively recruited patients, they will be contacted and data collected throughout their chemotherapy treatment and they will be contacted at 6 and 18 months post completion of chemotherapy to complete the questionnaires. Once this has been performed at the 18 month point post completion of chemotherapy their involvement in the study is complete and their routine medical follow up will continue unchanged.

7. STATISTICS AND DATA ANALYSIS

Sample size- prevalence and sampling for quality of life

Using estimates of physician documented prevalence of CIPN from the literature and the number of patients receiving oxaliplatin and taxanes annually in our population, the sample size is calculated using the formula for estimation of prevalence in a population: sample size = sn / (1+sn/N) and sn = z*z *p*q/(d*d) where p = probability, q=1-p, d= error acceptable, N = Available population and z=1.96 (Type 1 error of 5%) through an web-based sample size calculation program.

From January 1st 2010 to 31st December 2010 at Clatterbridge Centre for Oncology 804 patients received 3-weekly taxane treatment and 254 patients received oxaliplatin. Based on these annual figures we will need 219 patients who have received 3-weekly taxanes to demonstrate a rate of 40% +/- 5% of development of NCI CTC grade 2 or above peripheral neuropathy and 127 patients who have received oxaliplatin to demonstrate a rate of 20% +/- 5% of development of persistent grade 2 or greater cumulative peripheral neuropathy.

Sample size- pharmacogenetics

Statistical methodology for genetic association studies is a rapidly developing field, and the most up to date methods will be applied to bring the most powerful statistical methods to bear on the data analysis, and thus extract the maximum information possible from the genotype data. A detailed statistical analysis plan will be prepared prior to starting the analysis according to the individual characteristics of the SNP in question.

Prior to the association analyses, a test for Hardy Weinberg equilibrium will be undertaken at each SNP, using Fisher's exact test. Any marker found to deviate significantly ($p<0.001$) will be flagged and the reasons for deviation explored. Population substructure will also be tested for, and adjusted for in the analysis if any is detected. The extent of missing genotype data per SNP and per patient will be examined and the reasons for missingness explored. Tests to ensure that any missing genotype data is at random will also be conducted. Multiple imputation methods will be used should missing genotypes be extensive.

For assessing association between a SNP and the risk of neuropathy, two tests for association will be undertaken to compare genotype frequencies between cases and controls. The first will be a Chi-squared test, which makes no assumption regarding the underlying mode of inheritance, and the second will be a Cochrane-Armitage test for trend, which assumes an additive mode of inheritance. In the event that it is necessary to adjust for the effect of potential confounding factors, two logistic regression models will be fitted – the first including covariates to represent the confounding factors only and the second including covariates to represent both the confounding factors and the SNP – and a likelihood ratio test used to assess for association. The regression analysis will be conducted twice under the two different assumptions regarding mode of inheritance. In addition to the p-value, the false discovery rate will be calculated to assess for statistical significance whilst accounting for the multitude of tests undertaken.

In the event that copy-number variants (CNVs) are investigated in addition to SNPs, the most up to date methods to assess for association with CNVs will be applied.

As we are investigating a range of SNPs it is difficult to provide precise power calculations in advance. These will be based on the minor allele frequency (MAF) among controls and their effect size.

Combining these considerations we aim to recruit at least 219 taxane- treated patients and at least 127 oxaliplatin- treated patients prospectively in order to gain accurate, prospective data on incidence and quality of life. However, overall, combining prospectively and retrospectively recruited patients we would aim to involve as many patients as possible to ensure good power of the study to detect effects for both rare and common variants in pharmacogenetic analysis.

8. REGULATORY ISSUES

ETHICS APPROVAL

The study will be conducted in compliance with the guidelines of the Declaration of Helsinki on biomedical research involving human volunteers (Hong Kong revision, 1989 and the 48th General Assembly, Somerset West, Republic of South Africa, October 1996, updated in October 2000), ICH-GCP guidelines, relevant regulatory guidelines, and the study protocol. The protocol and relevant substantive data will be submitted for consideration by the Local Research Ethics Committee and written approval from the Chair of the Ethics Committee is required before the study is initiated and clinical activities of the study can commence.

Any major changes to the protocol will be made by means of a formal written protocol amendment and submitted for approval by the Research Ethics Committee. The Committee will also be kept informed of study progress and will receive a copy of the final study report.

R&D Trust Approval

This will also be confirmed prior to commencement of the study.

8.2 CONSENT

Written consent to enter the study will be sought from each participant only after a full explanation has been given, an information leaflet provided and time allowed for consideration. Signed participant consent will be obtained. Two copies of the consent form will be taken. The original signed copy will be kept in the study file, the first copy in the casenotes and the second will be offered to the patient. The right of the participant to refuse to participate without giving reasons will be respected. After the participant has entered the study the clinician remains free to give alternative treatment at any stage if he/she feels it is in the participant's best interest, but the reasons for doing so should be recorded. In these cases the participants remain within the study for the purposes of follow-up and data analysis. All participants are free to withdraw at any time from the protocol treatment without giving reasons and without prejudicing further treatment.

8.3 CONFIDENTIALITY

All patients CRFs, study related documentation and questionnaires will be labelled with a code so that no patient identifiable information is stored with this information. The key for this code will be kept in the site file and on a computer file on a password protected NHS computer accessible only to Clatterbridge Centre for Oncology employed clinical research staff.

The blood sample will be labelled with this same code to ensure that no patient identifiable information leaves Clatterbridge Centre for Oncology.

8.4 INDEMNITY

The NHS indemnity scheme will apply

8.5 SPONSOR

Clatterbridge Centre for Oncology NHS Foundation Trust
Clatterbridge Road,
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CH63 4JY
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8.6 FUNDING

CCO charitable trust is supporting the administrative costs of the study. Financial support for a clinical research fellow employed through Clatterbridge Centre for Oncology will be provided by Clatterbridge Cancer Research Trust. Financial support for the laboratory costs will be covered through the NHS Chair for Pharmacogenetics at the University of Liverpool.

8.7 AUDITS AND INSPECTIONS

The study may be subject to inspection and audit by CCO research governance personnel under their remit as sponsor and other regulatory bodies (e.g. for CTIMP's the MHRA) to ensure adherence to GCP, the NHS Research Governance Framework for Health and Social Care (2nd edition) and the Medicines for Human Use (Clinical Trials) Regulations (2004).

9. STUDY MANAGEMENT

The day-to-day management of the study will be co-ordinated through Clatterbridge Centre for Oncology. Data management and research practitioners will be utilised through Clatterbridge Centre for Oncology, ECMC and University of Liverpool.

11. PUBLICATION POLICY

Results will be intended for publication/presentation in clinical/scientific journals or meetings.
The results of the study will be fed back to the EORTC and may add to evidence of validation of the CIPN 20 module.

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APPENDICES

APPENDIX 1

NCI-CTC (version 3.0) neurotoxicity grading

Grade	1	2	3	4
Sensory	Loss of deep tendon reflexes or paraesthesia interfering with function but not activities of daily living	Sensory alteration interfering with function but not with activities of daily living	Sensory alteration interfering with activities of daily living	Disabling
Motor	Asymptomatic, weakness on examination/ testing only	Symptomatic weakness interfering with function but not with activities of daily living	Weakness interfering with activities of daily living. Assistance to walk indicated	Disabling

APPENDIX 2. SUMMARY OF INVESTIGATIONS, TREATMENT AND ASSESSMENTS

For prospectively recruited patients

Exam

	Pre-treatment/baseline	Cycle 3	Cycle 6	End of treatment (if >6 cycles)	6 months post completion	18 months post completion
blood	X					
EORTC QLQ C30	X	x	x	x	x	x
EORTC CIPN-20	X	x	x	x	x	x
informed consent	X					

For retrospectively recruited patients

Exam	
	Pre-treatment/baseline
blood	X
EORTC QLQ C30	X
EORTC CIPN-20	X
informed consent	X

PATIENT INFORMATION (VERSION 1.0, 20th June 2011)

You are being invited to take part in a research study aiming to investigate the effects of chemotherapy on the nerve endings which can cause changes in sensation. Before you decide if you want to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP/practice nurse if you wish. If there is anything that is not clear, or if you would like more information, please ask. This is a voluntary project, and if, when you have heard about the study, you would prefer not to take part your decision will be accepted without question and will not affect the standard of care you receive.

Why have I been chosen?

You have been invited to participate in this study as one of the recommended treatments for your condition involves a chemotherapy drug which can be associated with effects on the nerve endings. The medical term for this is peripheral neuropathy. Peripheral neuropathy can cause pins and needles or numbness in the hands and feet, weakness and sometimes pain. This possible side effect does not affect everyone and in those who are affected it often settles once the course of treatment ends. We know however that a small proportion of patients can continue to experience problems with peripheral neuropathy for months or years after the treatment has finished.

What is the purpose of the study?

Drug trials have given us some information about how commonly peripheral neuropathy occurs as documented and assessed by doctors and nurses. However, we want to be able to understand more about how many people it affects, how long it lasts for and what effects it has on every day life from a patients perspective.
Some of the symptoms of peripheral neuropathy can be hard to describe as it often involves trying to explain a sensation which can be difficult. Therefore what's recorded in patients' notes is the doctor's interpretation of the symptoms. This study is using a newly developed patient report questionnaire to try and gain better insight into this side effect. We would hope that this will help us in the future to give more accurate information to patients to aid decision making and also to see if using such a questionnaire is helpful in assessing this problem.
In addition, at present we are unable to predict who will be susceptible to peripheral neuropathy from chemotherapy. A second aim of this study is to see if it is possible to predict susceptibility to chemotherapy induced peripheral neuropathy. There is some evidence to suggest that side effects to some drugs may be determined by our genes (the basic building blocks of life). It is likely that more than one gene is going to be responsible. The purpose of this study is to identify some of these genes. We plan to look at a number of genes (including those responsible for enzymes responsible for breakdown of drugs, and those responsible for determining immune responses). As we do not know what genes are involved in toxic reactions to drugs, we have to test for many genes to identify the ones that may be important.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw from the study at any time without giving a reason. This will not affect the standard of care you receive in any way.

What will it involve for me if I take part?

There will be no change in the treatment you receive. As part of your routine care during your chemotherapy you will have regular contact with the medical and nursing team and we keep an eye for any symptoms of peripheral neuropathy. If you decided to take part you would be seen by a research nurse or other health professional who will take some details including your age, height, weight, ethnic origin, other medical conditions which may be associated with peripheral neuropathy, alcohol and smoking history. They will also record the condition for which you are receiving chemotherapy, the details of the treatment you are receiving and other drugs you are taking.
We would then, at intervals, ask you to complete questionnaires to assess your experience of any symptoms associated with your chemotherapy and their impact on your quality of life. You will be asked each time to complete two questionnaires, both are tools developed by the European Organisation for Research and Treatment of Cancer (EORTC). One is already in common use and the other, although it has been tried and tested is just starting to be used to more specifically find out more about patients experience of peripheral neuropathy. We will ask you to complete these questionnaires at the start of your treatment, after 3 months of treatment, at completion of your treatment and, thereafter, at 6 months and 18 months following completion of treatment.
We will also ask if you would be happy for us to take an additional blood sample when you're having your routine pre-chemotherapy blood tests in order to analyse it for a number of possible genetic signatures or variations which may be related to susceptibility to chemotherapy induced peripheral neuropathy.

If I participate will I have more visits to hospital?

No. Questionnaires can either be completed during your routine visit or we will post them out to you to save you having to come up to the hospital. Your blood test will occur during one of your routine visits.

What are the benefits of agreeing to participate?

If you agree to participate in the study unfortunately there are no direct benefits for you personally. Your treatment will be exactly the same as if you decide against participation. Your generosity in participating would however have the potential to benefit other patients in the future.

What are the possible disadvantages and risks of taking part?

Taking part in the study means completion of questionnaires which we would envisage taking 10-20 minutes to complete. If there are any questions that you would prefer not to answer you can choose not to.
It also means us taking one additional 9ml blood sample (about 2 teaspoonsful of blood). It can be uncomfortable to have a blood test and can cause minor bruising but we would aim for this to be taken at the same time that you are having your routine pre- chemotherapy blood tests so that you wouldn't have to have blood taken any more times than if you weren't taking part in the study. Taking part in the study will not affect your ability to obtain insurance for health purposes.

What happens if something goes wrong?

Any complaint about the way you have been dealt with during the study will be addressed by the medical team looking after you. If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions. Should you wish complain formally about any aspect of your care during the study the normal National Health Service complaints mechanisms will be available to you. If you wish to express a complaint or concern to someone outside the research team or your medical team the Patient Advice and Liaison Service (PALS) at Clatterbridge Centre for Oncology may be able to help on 0151 482 9727.

What will happen to my blood test?

Your blood sample along with all others taken for this study will be stored at the University of Liverpool. DNA will be extracted from the samples at the University and will be used to determine how your genes interact with the drug which can cause peripheral neuropathy and your susceptibility to drug reactions. Your sample will be stored at the University of Liverpool until it is used up.

It is important to note that all blood samples received by the University will be identified by a code number only. All coded clinical details will be kept securely, at Clatterbridge Centre for Oncology. Once the study has been completed, we will irreversibly anonymise your clinical details and blood sample, and therefore it will not be possible to trace the blood sample back to you. After anonymisation, it will also not be possible for you to withdraw the blood sample. Once anonymised, the DNA sample may be used for other research, but as this cannot be traced back to you, it will have no direct bearing on your clinical care. Further approval will be sought from the ethics committee for any future studies.

Your blood sample will be considered to be a gift to the University of Liverpool, which will act as custodian of all the samples obtained as part of this project. In some cases, a small amount of your sample will be provided to other researchers and may be sent to countries outside Europe. Future tests on the sample will be confined to tests for reactions to drugs only. However, it is important to remember that the sample will only be identified by a code.

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Will my participation mean my personal details are shared with others?

No. We will code your data so that staff outside of your treatment centre will not have access to your details. We will record a number of details and keep this linked to your coded completed questionnaires. These details will include your age, any pre-existing conditions such as diabetes which may also carry some risk of developing peripheral neuropathy, dates and details of your chemotherapy treatment and for what condition you are receiving it and your doctor's assessment of any symptoms or signs of peripheral neuropathy.

Can I withdraw consent?

Yes. Partipation is voluntary throughout. You are free to withdraw at any time.

What will happen to the results of the research study?

We will combine all the results from the patients taking part in the study, and publish any important results in medical journals. Data from this study may be shared with other researchers and potentially be used to develop ways to tailor treatment for future patients.

Who is organising and funding the research?

This study has been designed as a collaborative project by The University of Liverpool and Clatterbridge Centre for Oncology. The study is being funded by the Wolfson Centre for Personalised Medicine at the University of Liverpool, Clatterbridge Centre for Oncology Charitable Funds and Clatterbridge Cancer Research Trust.

Who has reviewed the study?
The study has been reviewed by the Local Research Ethics Committee.

Contact for further information

If you need further information or are worried about any aspect of the study, please do not hesitate to contact …..

…… (Research Nurse) on……

Or if you want more general, independent information on taking part in research, MacMillan Cancer Support may be able to help via their website, their local information centres or on the phone (0808 808 0000).

APPENDIX 4: CONSENT FORM

Clatterbridge Centre for Oncology NHS Foundation Trust

Clatterbridge cancer research understanding cancer

University of Liverpool

The Incidence, Impact on Quality of Life and Molecular Genetics of Chemotherapy Induced Peripheral Neuropathy

Name of principal investigator: *Dr Rosemary Lord*

In Collaboration with The University of Liverpool

PATIENT INFORMATION (VERSION 1.0, 20th June 2011)

You are being invited to take part in a research study aiming to investigate the effects of chemotherapy on the nerve endings which can cause changes in sensation. Before you decide if you want to participate, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with friends, relatives and your GP/practice nurse if you wish. If there is anything that is not clear, or if you would like more information, please ask. This is a voluntary project, and if, when you have heard about the study, you would prefer not to take part your decision will be accepted without question and will not affect the standard of care you receive.

Why have I been chosen?

You have been invited to participate as you completed a course of chemotherapy within the last 18 months with a chemotherapy drug which can be associated with effects on the nerve endings. The medical term for these effects is peripheral neuropathy. Peripheral neuropathy can cause pins and needles or numbness in the hands and feet, weakness and sometimes pain. This possible side effect will have been discussed with you when you were starting treatment. It does not affect everyone and in those who are affected it often settles once the course of treatment ends. We know however that a small proportion of patients can continue to experience problems with peripheral neuropathy for months or years after the treatment has finished.

What is the purpose of the study?

Drug trials have given us some information about how commonly peripheral neuropathy occurs as documented and assessed by doctors and nurses. However, we want to be able to understand more about how many people it affects, how long it lasts for and what effects it has on every day life from a patients perspective.
Particularly because some of the symptoms of peripheral neuropathy can be hard to describe as it often involves trying to explain a sensation which can be difficult. Therefore what's recorded in patients' notes is the doctor's interpretation of the symptoms. This study is using a newly developed patient report questionnaire to try and gain better insight into this side effect. We would hope that this will help us in the future to give more accurate information to patients to aid decision making and also to see if using such a questionnaire is helpful in assessing this problem.
In addition, at present we are unable to predict who will be susceptible to peripheral neuropathy from chemotherapy. A second aim of this study is to see if it is possible to predict susceptibility to chemotherapy induced peripheral neuropathy. There is some evidence to suggest that side effects to some drugs may be determined by our genes (the basic building blocks of life). It is likely that more than one gene is going to be responsible. The purpose of this study is to identify some of these genes. We plan to look at a number of genes (including those responsible for enzymes responsible for breakdown of drugs, and those responsible for determining immune responses). As we do not know what genes are involved in toxic reactions to drugs, we have to test for many genes to identify the ones that may be important.

Do I have to take part?

It is up to you to decide whether or not to take part. If you do decide to take part, you will be given this information sheet to keep and be asked to sign a consent form. You are still free to withdraw from the study at any time without giving a reason. This will not affect the standard of care you receive in any way.

What will it involve for me if I take part?

There will be no change in your treatment and follow up care you receive.
If you decided to take part you would be seen by a research nurse or other health professional who will take some details including your age, height, weight, ethnic origin, other medical conditions which may be associated with peripheral neuropathy, alcohol and smoking history. They will also record the condition for which you received chemotherapy, the details of the treatment you received, any symptoms of peripheral neuropathy you

had during your treatment and any symptoms you have now and also make a record of the other drugs you are were taking at the time of your chemotherapy.
You will then be asked to complete two questionnaires to assess your experience of any symptoms of peripheral neuropathy associated with your chemotherapy and their impact on your quality of life. Both of the questionnaires are tools developed by the European Organisation for Research and Treatment of Cancer (EORTC). One is already in common use and the other, although it has been tried and tested is just starting to be used to more specifically find out more about patients experience of peripheral neuropathy. You will only be asked to complete these questionnaires once.
We will then take a blood sample in order to analyse it for a number of possible genetic signatures or variations which may be related to susceptibility to chemotherapy induced peripheral neuropathy.
After this one visit your participation in the study is complete and your care will continue without any change.

If I participate will I have more visits to hospital?

If you are having routine follow up with your oncologist we will aim to arrange it so that any activities related to the study are carried out on the day of your routine appointment. We will avoid extra visits if possible and questionnaires can be sent out by post. If you are under the follow up care of your surgical team rather than routinely seeing your oncologist now that your treatment has finished we would need to arrange one visit to a Clatterbridge Centre for Oncology clinic in order to ask you to sign the consent form, collect the information detailed above and take the blood sample.

What are the benefits of agreeing to participate?

If you agree to participate in the study unfortunately there are no direct benefits for you personally. Your treatment will be exactly the same as if you decide against participation. Your generosity in participating would however have the potential to benefit future patients.

What are the possible disadvantages and risks of taking part?

Taking part in the study also means completion of questionnaires which we would envisage taking 10-20 minutes to complete which we would ask you to do a maximum of twice. If there are any questions that you would prefer not to answer you can choose not to.
It also means us taking one additional 9ml blood sample (about 2 teaspoonsful of blood). It can be uncomfortable to have a blood test and can cause minor bruising.
Taking part in the study will not affect your ability to obtain insurance for health purposes.

What happens if something goes wrong?

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APPENDIX 4: CONSENT FORM

Clatterbridge Centre for Oncology NHS Foundation Trust

Clatterbridge cancer research understanding cancer

University of Liverpool

The Incidence, Impact on Quality of Life and Molecular Genetics of Chemotherapy Induced Peripheral Neuropathy

Name of principal investigator: *Dr Rosemary Lord*

In Collaboration with The University of Liverpool

Please initial each box before signing the form:

1	I confirm that I have read and understood the information sheet dated ***Version 1, 20th June 2011*** for the above study	☐
2	I have had the opportunity to discuss the research and ask questions	☐
3	I understand that my participation is voluntary and I may withdraw up until the time that my blood sample can still be identified	☐
4	I understand that the results will not be added to my medical records	☐
5	I give permission to the researchers to have access to my medical records to extract information relevant to this study	☐
6	I agree to have a blood sample taken for tests on genes and other factors that determine how people react to drugs	☐
7	I understand that after the study is completed my sample will be anonymised and will be stored, and it will not be possible to trace the sample back to me	☐
8	I understand that my sample may be used in the future for more genetic tests as there are more scientific advances	☐
9	I agree to take part in the study	☐

.....	.....	.....
Name of patient	Date	Signature
.....	.....	.....
Name of person taking consent/ receiving form	Date	Signature

APPENDIX 5

Data to be collected for the CRF

- Date of birth
- Height
- Weight
- Ethnicity
- Chemotherapy details
    - Regimen
    - Intent
    - Cumulative dose
    - Details of any regimen or dose modifications

    - Dose delays
    - Number of cycles
    - Start and end dates of treatment
    - Any subsequent chemotherapy
- Primary diagnosis
- Concomitant medications (prescribed and over the counter)
- Allergies
- Co-morbidities
- Risk factors for peripheral neuropathy
- Symptoms and grading of peripheral neuropathy