A candidate gene study for oxaliplatin induced chronic peripheral neuropathy (OICPN) based on prior genome wide association study (GWAS)

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Background

Peripheral neuropathy complicates oxaliplatin therapy and occurs in two forms; a transient cold-induced neuropathy and a chronic form which requires dose reduction, early cessation, or causes long term morbidity in a proportion of patients. Various studies have suggested a complex pharmacogenetic susceptibility may exist to account for inter-individual variation in occurrence and severity of OICPN, but results are frequently contradictory or unvalidated.

We performed a systematic review of the literature which identified two East Asian studies suggesting a role for three SNPs; *ACYP2* (rs843748), *FARS2* (rs171401290), and *TAC1* (rs10486003), based on GWAS and subsequent replication in a candidate gene study. We attempted to replicate these findings in a Caucasian population.

Methods

A combined population from a prospective cohort study and retrospective case-control study was included for genotyping. All patients were of European ancestry, had no pre-existing symptomatic peripheral neuropathy and received oxaliplatin with a fluoropyridimine. They were assessed specifically for this study and categorised as ‘cases’ or ‘controls’ based on the presence and severity of OICPN using NCI CTC criteria. Cases experienced grade 3-4 neuropathy or grade 2 neuropathy resulting in adjustment or cessation of oxaliplatin. Controls experienced a maximum of grade 1 neuropathy with no treatment adjustments required due to OICPN. Minimum cumulative dose criteria were applied to inclusion of controls. Blood or saliva samples were collected, DNA extracted and genotyped for the selected SNPs using the TaqMan allelic discrimination methodology.

Results

After quality control, 119 of 120 eligible recruited patients were included in the final genotyping results comprising 51 controls and 68 cases. None of the three SNPs were found to be associated with development of OICPN on univariate analysis or after adjustment for potentially relevant clinical factors (P>0.05).

Conclusion

Our findings fail to support the suggested relationship between the included SNPs and development of clinically important OICPN in European patients.