**Abstract**

Tyrosine kinase inhibitors are widely utilised in veterinary oncology for the treatment of mast cell and solid tumours. In man, these drugs are associated with thyroid dysfunction: however, to date only one study has investigated this in dogs. The aim of this study was to prospectively assess thyroid function in a group of dogs receiving toceranib.

Thirty-four dogs were prospectively enrolled at two referral hospitals, into two groups; those receiving toceranib with prednisolone and those receiving toceranib alone. Total thyroxine (T4) and thyroid stimulating hormone (TSH) was monitored at regular time points during treatment. Follow up data was available for 19 dogs. Overall, 12 incidences of elevated TSH occurred but none of these dogs had concurrent low T4 concentrations.Hypothyroidism was not diagnosed in any patient. Patient drop-out was higher than anticipated which prevented the assessment of long term toceranib administration on thyroid function.

Overall short-term toceranib therapy is not associated with hypothyroidism but does result in elevations in TSH.

**Introduction**

Receptor tyrosine kinases (RTK) are cell membrane proteins through which the majority of growth factors mediate their effects. RTK activation mediates many processes including cell growth, survival, neovascularisation and tissue repair. RTK activation is normally rigorously controlled, but dysregulation in neoplasia can lead to uncontrolled cell proliferation, aberrant cell survival and tumour neovascularisation. Tyrosine kinase inhibitors (TKI) were developed to block specific pathway activation. The first TKI (imatinib) was developed in the mid-1990s for the treatment of chronic myeloid leukaemia in man (Druker et al., 1996). TKIs have subsequently been developed to treat numerous humans neoplasias including chronic myeloid leukaemia, metastatic hepatocellular carcinoma, renal cell carcinoma, non-small cell lung cancer and breast cancer.

Toceranib is a TKI licenced for the treatment of canine mast cell tumours (Pryer et al., 2003). Studies have documented that toceranib has therapeutic action in other canine tumours (London et al., 2012, Bernabe et al., 2013).Toceranib has multiple molecular targets including KIT, VEGFR, PDGFR and RET - many of which are activated in a variety of canine neoplasias (Urie et al., 2012, Santos et al., 2016, Hayes et al., 2013, Arico et al., 2014).

Due to the prevalence of RTKs in the body, inhibition of non-target RTKs causes a variety of adverse effects, the most common of which for toceranib are diarrhoea, myelosuppression, lethargy and skin rashes (London et al., 2012). These are usually tolerable in dogs. However, more serious effects include renal toxicity, hepatoxicity, hypertension and gastrointestinal perforation (Tjostheim et al., 2016, Bernabe et al., 2013, London et al., 2003). Endocrine abnormalities, particularly thyroid dysfunction, are widely reported in people receiving TKIs. The mechanisms of TKI-mediated hypothyroidism may include inhibition of VEGFR-2 leading to thyroid capillary regression (Baffert et al., 2006); inhibition of thyroid peroxidise (Wong et al., 2007); destructive thyroiditis and decreased uptake of iodine by the thyroid gland (Mannavola et al., 2007). The reported incidence of hypothyroidism in human patients treated with sunitinib, a drug similar to toceranib in its targets, is high (18-86%), with a significant proportion of clinically normal patients also having altered thyroid function tests (Rini et al., 2007, Desai et al., 2006, Tamaskar et al., 2008). Clinical signs of hypothyroidism in man include psychological disorders, lethargy, hypothermia and cardiac arrhythmias, and untreated hypothyroidism contributes to poor quality of life. In hypothyroid cancer patients, these signs may be erroneously attributed to the primary disease or treatment rather, yet hypothyroidism can be easily treated with levothyroxine. It is recommended that all human patients receiving TKIs have regular thyroid function tests (Torino et al., 2009). As clinical signs of hypothyroidism can be insidious in dogs and may be attributed to neoplasia, or toceranib-induced lethargy, cases of iatrogenic hypothyroidism may be underdiagnosed.

Toceranib was developed simultaneously with sunitinib and they share similar adverse effects. However, to date there has only been one study documenting effects on the canine hypothalamic-pituitary-thyroid axis: in this cohort no dogs developed hypothyroidism over a short period, although alterations in both free T4 and TSH were seen (Hume et al., 2018).

The aim of this prospective cohort study was to monitor thyroid function in a prospectively enrolled cohort of client owned dogs receiving toceranib in order to assess for iatrogenic hypothyroidism.

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**Methods**

Dogs were prospectively recruited and enrolled from two UK referral hospitals between 2014 and 2016. Dogs had to meet the following criteria; a cytological or histological diagnosis of neoplasia; an expected life expectancy of at least two months with no significant co-morbidities; no concurrent medication which may affect thyroid function values (including but not limited to potentiated sulphonamides, phenobarbital, cimetidine or amiodarone) and no thyroid-related illness (including thyroid neoplasia). Dogs were included if they had received previous treatment (surgery/chemotherapy) although a minimum wash-out period of one week was necessary between previous chemotherapy and toceranib. Concurrent treatment with prednisolone was allowed as this was considered standard of care for some tumours (e.g. mast cell tumour). Dogs were divided into two groups – those that were receiving both prednisolone and toceranib and those that were receiving toceranib alone to assess for any potential effect on thyroid function from prednisolone therapy.

The study design was approved by the institution’s ethics committees and informed owner consent was obtained prior to enrolment. Monitoring of dogs receiving toceranib involved clinical examination, and sampling for haematology, biochemistry and urinalysis to assess for known toxicities. Routine monitoring tests were performed as per the data sheet or at the discretion of the attending clinician. This was planned for day 0, day 14, day 28 and then day 56. Further samples were collected approximately every 28 days for the remainder of the treatment. At monitoring visits, surplus serum was used to measure serum TSH and T4 to monitor thyroid function (Siemens Immulite 200i using canine specific kits). Concurrent toxicities were also recorded and graded using the Veterinary Comparative Oncology Group (VCOG)(VCOG, 2011).

Dogs were removed from the study if they had disease progression warranting a change in treatment prior to second sample collection, if toceranib treatment was withdrawn prior to second sample collection or if the owner withdrew consent.

**Statistical analysis**

A power calculation was performed to determine the number of dogs required to detect a significant discrepancy between 100% normal thyroid tests and 50% normal, to achieve a power of 0.9 (with p=0.05). This showed that 15 dogs were required per group. Given an estimated dropout rate of 25% (due to expected treatment failures) the aim was to recruit 20 dogs to each group.

Data distribution was assessed for each variable (T4, TSH) for each group (prednisolone and prednisolone + toceranib) at each time point. For dogs where testing fell outside the set time points the values were rounded to the nearest check-point. Significance was determined as p=0.05. Data was assessed for distribution and then a Wilcoxon rank test was performed to assess differences in data sets at each time point as appropriate. Results from dogs receiving prednisolone were compared with those that are not. To test differences between groups a t-test/Kruskal-Wallis test was performed as appropriate, depending on the distribution of the data.

**Results**

Overall 34 dogs met the inclusion criteria and were enrolled onto the trial over the planned study period. Of these, 15 dogs had insufficient data for follow-up, leaving 19 dogs for analysis. Six dogs were in the mast cell group while 13 dogs were in the ‘other neoplasia’ group. The most common other tumour was anal sac adenocarcinoma (5 dogs) followed by pulmonary carcinoma (2 dogs). There was one each of sebaceous carcinoma, nasal carcinoma, mammary tumour, squamous cell carcinoma of the vulva and extra-skeletal osteosarcoma (table 1). The most common breed was cross breed (5) followed by cocker spaniel (3), Labrador (2), Staffordshire bull terrier (2) and one each of beagle, Yorkshire terrier, Border terrier, Jack Russel terrier, Bassett hound, Irish setter and wheaten terrier. Median age was 9 years (range 6-12). Two dogs in the ‘other neoplasia’ group received prior chemotherapy (alternating carboplatin and mitoxantrone for anal sac adenocarcinoma) while in the mast cell group one dog received prior vinblastine and one dog received prior radiotherapy.

Toceranib was prescribed on a Monday-Wednesday-Friday or every other day dosing regimen. Median toceranib dose administered was 2.8mg/kg (range 2.44-3.03). All of the dogs with mast cell tumour disease received concurrent prednisolone (1mg/kg).

With regard to thyroid function (Table 1), median baseline total thyroxine was 24.8 nmol/L (range 7.8-50.5, RI: 5-44) while median baseline TSH was 0.158 ng/ml (range 0.02-0.626, RI: 0.03-0.5). Following the baseline measurements, thyroid function testing was performed in each patient a median of two further times (range 1-5). Overall, twelve incidences of elevated TSH occurred, with 10/12 cases occuring after six weeks of therapy. Median TSH at week six was 0.377 ng/ml. There was a significant difference (*p*  = 0.0061) between baseline TSH and median TSH at week six (figure 1). There was no significant difference between baseline thyroxine and week six.

The highest mean TSH concentration was recorded at week 12 (0.48 ng/ml, range 0.114-3.66 RI: 0.03-0.5). However none of the dogs with elevated TSH had an abnormally low T4 and therefore no patients were diagnosed with hypothyroidism during the study period. Only three incidences of elevated TSH occurred in the prednisolone + toceranib group however follow-up data beyond 12 weeks was only available for two dogs as the majority of dogs with mast cell tumour disease developed progressive disease. There were insufficient cases to compare thyroid function between the two groups.

Six of the dogs (6/19) developed other toxicities during toceranib adminstration. The most common was proteinuria (3/6) followed by VCOG grade I-II gastro-intestinal toxicity (2/6). No dogs stopped therapy due to toxicity.

Table 1

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Case number | Age (m) | Breed | Sex | Tumours | Toceranib dose | Baseline T4 | Baseline TSH | T4 @ 2 weeks | TSH @ 2 weeks | T4 @ 6 weeks | TSH @ 6 weeks | T4 @ 12 weeks | TSH @ 12 weeks | T4 @ 18 weeks | TSH @ 18 weeks | T4 @ 30w | TSH @ 30w | T4 @ 34w | TSH @ 34w |
| 1 | 74 | Beagle | MN | Metastatic sebaceous carcinoma | 2.87 | 24.8 | 0.078 | N/A | N/A | 39.1 | 0.435 |  |  |  |  | 30.8 | 0.736 | 28.2 | 0.396 |
| 2 | 129 | Labrador | FN | ASAC | 2.45 | 31.4 | 0.541 | 24.6 | 0.399 |  |  |  |  |  |  |  |  |  |  |
| 3 | 84 | Cross Breed | MN | Nasal carcinoma | 2.84 | 35.3 | 0.101 | 26.6 | 0.618 | 15.1 | 1.33 | 5.65 | 3.66 |  |  | 25.9 | 0.556 | 20.2 | 0.263 |
| 4 | 120 | Cross Breed | MN | Pulmonary carcinoma | 2.87 | 24.7 | 0.243 | 34.9 | 0.258 |  |  |  |  |  |  |  |  |  |  |
| 5 | 88 | Yorkshire Terrier | FN | mammary carcinoma | 2.94 | 34.2 | 0.062 | 27.8 | 0.199 | 36.4 | 0.09 |  |  |  |  |  |  |  |  |
| 6 | 72 | Xbreed | FN | MCT | 3.01 | 25 | 0.02 | 26 | 0.019 |  |  |  |  |  |  |  |  |  |  |
| 7 | 139 | Cocker Spaniel | MN | Pulmonary carcinoma | 2.44 | 21.5 | 0.076 | 27.3 | 0.124 | 24.8 | 0.175 | 22.9 | 0.712 |  |  |  |  |  |  |
| 8 | 93 | Border Terrier | MN | MCT | 2.56 | 27.2 | 0.158 |  |  | 15.3 | 0.236 |  |  |  |  | 10.8 | 0.233 | 25.1 | 0.256 |
| 9 | 72 | JRT | FN | MCT | 2.82 | 27.9 | 0.048 |  |  | 41.1 | 0.037 | 34.4 | 0.114 |  |  |  |  |  |  |
| 10 | 108 | Basset Hound | MN | MCT  | 2.8 | 50.5 | 0.336 | 40.3 | 0.349 | 39.4 | 1.01 |  |  |  |  |  |  |  |  |
| 11 | 149 | Cross Breed | FN | SCC (vulva) + metastatic mammary carcinoma | 3.03 | 15.4 | 0.626 |  |  | 13.4 | 1.15 | 19.2 | 2.62 |  |  |  |  |  |  |
| 12 | 125 | Labrador | FN | MCT | 2.77 | 7.8 | 0.131 | 40.7 | 0.23 | 40.5 | 0.171 | 36.8 | 0.265 |  |  | 31.9 | 0.19 | 27.9 | 0.373 |
| 13 | 132 | SBT | MN | OSA (extra-skeletal) | 2.78 | 37.3 | 0.389 | 28.6 | 0.604 |  |  |  |  |  |  |  |  |  |  |
| 14 | 116 | Irish Setter | ME | ASAC | 2.68 | 30.6 | 0.05 |  |  |  |  |  |  |  |  | 17.4 | 0.133 | 26.4 | 0.465 |
| 15 | 101 | Wheaten Terrier | MN | Carotid body tumour | 2.84 | 10.3 | 0.26 | 11.9 | 0.452 | 9.94 | 0.925 | 8.57 | 0.48 |  |  |  |  |  |  |
| 16 | 101 | Xbreed | ME | MCT + heart base mass with metastasis to lungs | 2.6 | 12.7 | 0.372 | 14.4 | 0.762 | 10.8 | 0.788 |  |  |  |  |  |  |  |  |
| 17 | 136 | SBT | ME | ASAC with metastasis to local lymph nodes | 2.7 | 19.2 | 0.559 |  |  | 13.6 | 0.271 |  |  | 14.9 | 0.33 |  |  |  |  |
| 18 | 144 | Cocker | MN | ASAC, metastasis to lymph node and lungs | 3 | 15.8 | 0.265 |  |  | 22 | 0.377 |  |  | 23 | 0.7 | 28.2 | 1.38 |  |  |
| 19 | 100 | Cocker |  | ASAC, metastasis to spleen + lymph nodes | 2.3 | 24.3 | 0.147 |  |  |  |  | 20.6 | 0.201 | 22.4 | 0.349 |  |  |  |  |

Table 1:

Key

ASAC = anal sac adenocarcinoma

MCT = mast cell tumour

OSA = osteosarcoma

SCC = squamous cell carcinoma

**Discussion**

Hypothyroidism is a common complication in human patients receiving TKIs (Rini et al., 2007, Desai et al., 2006) and the aim of this prospective study was to assess whether it occurred in dogs. This study failed to identify hypothyroidism in any dog receving toceranib during the observation period, but identified elevations in TSH in nine of fifteen dogs (total of 12 incidences).Elevations in TSH without T4 depression have been reported both in people receiving sunitinib (Desai et al., 2006) and in the recent study of dogs receiving toceranib (Hume et al., 2018). While elevated TSH can occur due to non-thyroidal illness, this is uncommon: a frequency of 8.1% has been reported (Kantrowitz et al, 2001, Javma). Indeed, some studies report that all euthyroid dogs (in a cohort with signs compatible with hypothyroidsim) have normal TSH (Boretti and Reusch, 2003). Elevated TSH may be a precursor to hypothyroidism, and several patients showed increasing TSH over time: a potential reason for hypothyroidism not developing in this population may be the short follow-up , which was unavoidable due to the clinical situation, with treatment being withdrawn when progressive disease was evident.

There are conflicting reports in the human literature regarding the onset of hypothyroidism; Rini et al reported that altered T4/TSH occurred after a median of 2 cycles of sunitinib (i.e. 2 months) whereas other studies reported that hypothyroidism was more likely to occur after around 11-12 months (Desai et al., 2006, Rini et al., 2007, Clemons et al 2012). In our cohort, only 6 patients had T4/TSH measured at weeks 30 and 34, limiting the power of the study. Interestingly, two dogs that had previously had elevated TSH had normal TSH at this time point: it is unclear if this is a reflection of severe non-thyroidal illness at this time point, or perhaps an ability to normalise the hypothalamus- pituitary-thyroid (HPA) axis over time.

As the median duration of treatment with toceranib in dogs is in the region of 19-25 weeks it is possible that this timeframe is too short to signficantly affect thyroid function (Laver et al., 2018, London et al., 2012). The findings of the current study support those previously reported by Hume et al (2018) which also followed the study cohort for a relatively short period of time but concluded there was disruption of the HPA with similar increases in TSH (Hume et al., 2018).

Unfortunately the study was underpowered due to slow recruitment and higher than anticipated drop out rate (44% rather than 25%). This is attributed to a combination of rapid disease progression in some dogs (particularly those with aggressive mast cell tumours) and failure to follow up, as many dogs had further monitoring and treatment performed at their primary vet due to client preference. Funds were not available to rectruit additional cases. As only six dogs were recruited to the first treatment group (toceranib and prednisolone) it is also unclear what effect, if any, prednisolone may have on thyroid function in these dogs. It has previously been established that prednisolone administration can sginificantly decrease serum thyroxine concentrations in healthy dogs (Torres et al., 1991), though none of these dogs had thyroxine levels below the lower limit of the reference interval.

In conclusion, this study has not identified an association between short term toceranib administration and hypothyroidism in dogs. However, there was a significant increase in TSH in patients treated with this drug and further studies with a greater number of dogs that are receiving treatmnt and are followed for a prolonged period are required to improve understanding of the effect of toceranib phosphate on thyroid function in dogs.

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