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Toxicity and response in cats with neoplasia treated with toceranib phosphate

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Abstract

Objectives Toceranib phosphate is a tyrosine kinase inhibitor licensed for the treatment of non-resectable Patnaik grade II/III recurrent cutaneous mast cell tumours in dogs. There is no information in cats regarding the tolerated dose, toxicity or tumour response of this drug. The aim of this study was to analyse retrospectively a cohort of cats with advanced neoplasia treated with toceranib to identify toxicity and response.

Methods The medical records of the Small Animal Teaching Hospital were reviewed. Cats were included if they had received toceranib for at least 2 weeks for the treatment of histologically or cytologically confirmed neoplastic disease, and had at least one set of monitoring blood tests (haematology, biochemistry) performed after baseline tests. Toxicity was graded according to the Veterinary Comparative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) and response was measured according to Response Evaluation In Solid Tumors (RECIST) criteria.

Results Fourteen cats met the inclusion criteria, the majority of which (13/14) had received previous therapy (surgery, radiotherapy, chemotherapy). The most common tumour types were mast cell tumours or malignant epithelial tumours. Toxicity occurred in 10/14 cats – 10 cats had mild myelosuppression or gastrointestinal effects. Two cats developed severe hepatoxicity. One cat died from congestive heart failure, although whether this was related to toceranib therapy is unknown. Regarding response, one cat achieved complete response; two cats achieved partial response and five cats achieved stable disease: overall biological response rate was 57.1%. All of the cats that achieved either partial or complete response were treated for mast cell disease. Overall median duration of response was 90 days (range 14–570 days). None of the cats with squamous cell carcinoma achieved a response.

Conclusions and relevance Toceranib phosphate is generally well tolerated in cats, with toxicity limited to mild gastrointestinal or myelosuppressive effects in the majority of cases (10/14) in this study; however, hepatotoxicity is a concern. Response to treatment in this small cohort was similar to that reported in dogs.

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Introduction

Toceranib phosphate (Palladia; Zoetis) belongs to the class of drugs known as tyrosine kinase inhibitors (TKIs) and has a wide variety of molecular targets, including KIT, vascular endothelial growth factor receptor 2, platelet-derived growth factor receptor and Flt-3. Interruption of these molecular pathways results in inhibition of cell growth, cell death and apoptosis.[1,2] Toceranib phosphate has been licensed in Europe since 2009 for the treatment of non-resectable mast cell tumours in dogs. Recent studies in dogs have reported that toceranib may have action in other solid tumours, including anal sac adenocarcinoma and osteosarcoma.[3] This is also supported by the use of its sister drug (sunitinib) in human oncology for the primary treatment of renal carcinoma.[4] However, as yet, there is very limited data regarding the use of toceranib in the treatment of feline neoplasia.

The toxicity profile of toceranib is relatively well known in dogs. The most commonly reported effects are

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gastrointestinal (GI; anorexia, vomiting, diarrhoea) and myelosuppression.[5,6] These effects are generally mild and self-limiting, although occasionally require dose reductions or 'treatment holidays'. However, many other toxicities have been reported, including hepatotoxicity, proteinuria and myopathies, which reflect the wide array of potential targets for the drug in the body. Endocrinopathies and cardiotoxicity have also been reported in human beings treated with sunitinib, although these have not yet been established in dogs.[7–9] There are no published reports of the tolerability of toceranib treatment in cats. A prospective study evaluated the toxicity in cats treated with masitinib (another veterinary licensed TKI), which reported effects similar to dogs, mainly mild GI events and myelosuppression.[10]

The aim of this study was to report the toxicity profile in cats with a variety of tumours treated with toceranib. A secondary aim of the study was to assess tumour response to therapy.

Materials and methods

The study design was approved by the University of Liverpool Veterinary Research Ethics Committee. The clinical records of the Small Animal Teaching Hospital, University of Liverpool, were reviewed between 2009 and 2014. Cats were included in the study if they had received toceranib phosphate for at least 2 weeks for the treatment of histologically or cytologically confirmed neoplastic disease, and had at least one set of monitoring blood tests (haematology, biochemistry) performed. All cats had baseline haematology and biochemistry on day 0 prior to therapy. In general, therapeutic monitoring (haematology, biochemistry) was performed after the first 2 weeks of therapy and then monthly thereafter (in accordance with the recommended monitoring for dogs as per the data sheet). Adverse events were categorised by the Veterinary Comparative Oncology Group – common terminology criteria for adverse events (VCOG-CTCAE) grading system where appropriate (Table 1). Cats with significant alterations in haematology and/or biochemistry (equivalent to a VCOG grade I alteration; Table 1) or significant clinical signs before starting treatment with toceranib were excluded, with the exception of cats that had stable chronic kidney disease. Prior therapy (surgery, chemotherapy, radiotherapy) was allowed, although a washout period of 7 days was required from previous chemotherapy to starting toceranib. Concurrent treatment with corticosteroids, non-steroidal anti-inflammatory drugs or symptomatic treatments (eg, famotidine, maropitant) was allowed. Tumour response was graded according to Response Evaluation In Solid Tumors (RECIST) criteria,[11] where possible, based on measureable cutaneous or oral lesions (complete restaging with thoracic radiography and abdominal ultrasound or CT was only performed in 4/14 cats – all of these cats had no gross external disease to monitor response). Response was classified as either complete or partial. Stable disease (of a duration of $\geqslant$4) was also considered a response, in line with previous studies reporting response to TKIs and RECIST criteria.[6]

Results

The database search returned 18 cats that had received toceranib between January 2009 and June 2015. Of these, four were excluded; three cats had rapidly progressive disease and no follow-up, while the fourth had significant GI signs prior to the onset of therapy. Fourteen cats were therefore available for analysis. The majority (12/14) were domestic breeds, with one Ragdoll and one Maine Coon. Median age at onset of toceranib therapy was 120.5 months (range 44–204 months). A range of neoplasms were represented (Table 2), although most were either of mast cell or epithelial origin. The majority (13/14) of the cats had received at least one form of previous treatment, including surgery, radiotherapy and/or chemotherapy, and had advanced disease (disseminated or metastatic disease) at the time of starting treatment (see Table 1).

The median dose of toceranib administered was 2.78 mg/kg (range 1.9–3.8 mg/kg). All but one of the cats received toceranib on a Monday–Wednesday–Friday basis; the remaining cat received the drug twice weekly, owing to its small size and concern regarding overdose. The median duration of therapy in all cats was 40 days (range 14–570 days). Nine of 14 cats received some form of concurrent treatment: eight cats were also treated with prednisolone on non-toceranib days and one cat received meloxicam (Metacam; Boehringer Ingelheim) on the non-toceranib days. All of the cats receiving concurrent prednisolone had mast cell disease, and all of these cats had previously received prednisolone prior to starting toceranib.

Ten of 14 cats exhibited some form of toxicity during treatment. Mild haematological changes were seen in five cats. Four cats had VCOG grade 1 neutropenia (Table 1), while two cats had mild lymphopenia (ranges 0.3–0.6 $\times$ 10^9 cells/l; reference interval 1.5–7.0 $\times$ 10^9 cells/l). One of these cats had persistent lymphopenia for 2 months and also had an episode of neutropenia. Biochemical changes were seen in five cats. Elevations in liver enzymes were seen in three individuals – one cat had a VCOG grade 1 increase in alkaline phosphatase, while, more significantly, two cats demonstrated VCOG grade 4 elevation (ie, a more than two-fold increase compared with the upper reference value) in alanine transaminase (ALT). In these cats, toceranib therapy was discontinued, but ALT remained elevated. However, neither cat demonstrated clinical signs of a hepatopathy. Two cats demonstrated transient elevations in kidney parameters – one cat had VCOG grade 1 elevation in urea, while the other cat had a

Table 1 Veterinary Comparative Oncology Group adverse events (modified)*

Adverse event	Grade				
	1	2	3	4	5
Neutropenia	1500 µl to LLN	1000–1499 µl	500–999 µl	<500 µl	Death
ALP	ULN–1.25 × ULN	1.25–1.5 × ULN	1.5–2 × ULN	>2 × ULN	–
ALT	ULN–1.25 × ULN	1.25–1.5 × ULN	1.5–2 × ULN	>2 × ULN	–
Urea	ULN–1.5 × ULN	1.5–2 × ULN	2–3 × ULN	>3 × ULN	–
Creatinine	ULN–1.5 × ULN	1.5–2 × ULN	2–3 × ULN	>3 × ULN	–
Vomiting	<3 episodes in 24 h, medical intervention not indicated	3–10 episodes in 24 h; <5 episodes/day for ⩽48 h; parenteral fluids (IV or SC) indicated ⩽48 h; medications indicated	Multiple episodes >48 h and IV fluids or PPN/TPN indicated >48 h	Life-threatening (eg, haemodynamic collapse)	Death
Diarrhoea	Increase of up to two stools per day over baseline; no increase in frequency; however, consistency decreased over baseline	Increase of 3–6 stools per day over baseline; medications indicated; parenteral (IV or SC) fluids indicated ⩽48 h; not interfering with ADL	Increase of >6 stools per day over baseline; incontinence >48 h; IV fluids >48 h; hospitalisation; interfering with ADL	Life-threatening (eg, haemodynamic collapse)	Death
Alopecia	Sparse thinning or denuding of hair at localised site, patchy alopecia	Generalised thinning of haircoat, generalised alopecia	–	–	–

*Adapted from the Veterinary Comparative Oncology Group – common terminology criteria for adverse events (VCOG-CTAE) following chemotherapy or biological antineoplastic therapy in dogs and cats
ALP = alkaline phosphatase; ALT = alanine transaminase; LLN = lower limit of normal; ULN = upper limit of normal; IV = intravenous; SC = subcutaneous; PPN = partial parenteral nutrition; TPN = total parenteral nutrition; ADL = activities of daily living

VCOG grade 1 increase in creatinine. No urinalysis was available and in both cats the parameters returned to normal – the cat with elevated creatinine had a 1 week treatment holiday, and no intervention was performed on the cat with elevated urea. GI toxicity was observed in five cats as follows; one episode of VCOG grade 2 vomiting in one cat which necessitated a treatment break; two individual episodes of VCOG grade 1 diarrhoea in two cats, intermittent VCOG grade 1 vomiting in one cat and GI ileus in one cat. A further cat with an oral squamous cell carcinoma (SCC) became anorexic, although this was attributed to tumour progression rather than toceranib therapy. None of the toxicities recorded required hospitalisation and the GI toxicities were managed symptomatically. None of the cats experienced concurrent vomiting and diarrhoea. One of the cats developed VCOG grade 1 alopecia, which did not require alteration of treatment. Furthermore, an additional cat developed congestive heart failure after 90 days of treatment and was euthanased.

In terms of response to therapy, only one cat achieved a complete response (CR). Two of the cats achieved a partial response (PR), while five cats achieved stable disease, leading to an overall biological response of 8/14 (57.1%). One cat was censored as it was alive at time of analysis. Overall the median duration of response was 90 days (range 14–570). The three cats that either achieved CR or PR were all undergoing treatment for mast cell disease. The three cats receiving toceranib for SCC did not show a response to therapy.

Discussion

This retrospective study identified a group of cats with advanced neoplastic disease that were treated with toceranib phosphate. The median dose prescribed correlated well with that previously reported to be effective in dogs.[6] As with many dogs treated with toceranib, the majority of these cats had already received multimodal therapy, including surgery, radiotherapy and previous cytotoxic chemotherapy.

The toxicity profile of the cats treated in this study is similar to that previously reported for dogs using a similar dose of toceranib.[6] The majority of events were mild (VCOG grade 1) neutropenia or GI upset, which did not require hospitalisation or treatment delays. Of more concern were the two cats that developed VCOG grade 4 elevations in ALT, although neither cat demonstrated clinical signs attributable to liver disease. Although mild increases in ALT have been reported in dogs and

Table 2 Patient information

Case number	Age (years)	Sex	Breed	Tumour type	Disease burden
1	4.8	MN	Maine Coon	Disseminated cutaneous MCT	Multiple cutaneous lesions with nodal involvement
2	14.1	MN	DSH	Oral SCC + visceral MCT	MCT in liver and inguinal nodes
3	8.6	MN	Ragdoll	Cutaneous MCT	MCT metastasis to liver and spleen
4	8.8	FN	DSH	Oral MCT	MCT metastasis to liver, spleen and abdominal lymph nodes
5	13.9	FN	DLH	Cutaneous MCT	Metastasis to local lymph node
6	10.8	MN	DSH	T-cell intestinal lymphoma	Intestine + abdominal lymph nodes
7	3.7	FN	DSH	Metastatic mammary adenocarcinoma	Pulmonary nodules and recurrent mammary mass
8	9.3	MN	DSH	Cutaneous MCT	Metastasis to submandibular lymph nodes and spleen
9	8.0	MN	DSH	Ceruminous gland adenocarcinoma	Metastasis to local lymph nodes
10	11.6	MN	DSH	Anaplastic mucocutaneous MCT	Metastasis to spleen and skin
11	13.8	FN	DSH	Anal SCC	Metastasis to sublumbar and colic lymph nodes
12	17.0	FN	DSH	Mandibular SCC	No metastasis
13	9.3	FN	DSH	Mammary carcinoma	Multiple cutaneous metastatic nodules
14	15.9	FN	DSH	Salivary gland carcinoma	No metastasis

MN = male neutered; MCT = mast cell tumour; DSH = domestic shorthair; FN = female neutered; DLH = domestic longhair; SCC = squamous cell carcinoma

humans,[5,6,12] this severe degree of ALT elevation may be species specific, which may be related to the impaired glucoronidation mechanism in cats. Both of these cats received a higher-than-median dose of toceranib (3.08 mg/kg and 3.8 mg/kg), indicating a possible dose-dependent mechanism of toxicity. Importantly, ALT elevations remained high, despite cessation of treatment in both cats. Although disease progression as a cause of the elevated ALT cannot be excluded, it is considered less likely, as both cats had large elevations in ALT within 4 weeks of starting toceranib therapy.

Cardiotoxicity is a recognised toxicity of sunitinib in humans with arrhythmias and decreased left ventricular ejection fractions being reported – these effects are often reversible on cessation of therapy.[7,13] The mechanism of action is thought to be sunitinib-mediated depletion of cardiac pericytes.[14] In this study, one cat died from congestive heart failure after 90 days of toceranib therapy. The cat had no previous history of heart disease; however, pretreatment echocardiography was not performed and therefore subclinical hypertrophic cardiomyopathy could not be excluded. It is reported in the human literature that patients are more likely to develop congestive heart failure with pre-existing cardiac pathology, which may be pertinent to cats with subclinical hypertrophic cardiomyopathy.[8] The prevalence of heart disease in the general UK cat population is unknown – reports in smaller populations of cats have reported the prevalence of hypertrophic cardiomyopathy at 8–15%.[15–17] The cat in question may therefore have progressed with clinical heart disease, even in the absence of toceranib treatment. Further prospective studies with a larger number of patients are needed to monitor cardiac function over time in cats treated with toceranib.

In dogs, the biological response to toceranib when treating a variety of solid tumours is reported to be 54–74%.[1] The biological response rate in this cohort of cats was 57.1%, which would correlate with that previously reported. For the cats with mast cell disease (n = 6) only two cats did not show any response to therapy, resulting in a biological activity of 67% for the remainder, which is similar to that previously reported for dogs with mast cell disease.[4] However, the survival times for the cats were short, which may reflect the advanced stage of the disease or species differences in the sensitivity of mast cell neoplasia. The KIT mutation status of the tumours was unknown. Nevertheless, three of the treated cats with mast cell disease lived longer than 2 months.

Conclusions

Toceranib phosphate is well tolerated in cats, with the majority of individuals having VCOG grade I neutropenia or gastrointestinal signs. Potential hepatotoxicity is

of concern and may correlate with dose administered. Furthermore, elevations in ALT persisted in two cats after the cessation of therapy. Cardiac disease developed in one cat. Although this may have been coincidental, prospective trials are required to monitor systolic function in cats receiving toceranib therapy to assess whether there is cardiotoxicity. In addition, further work investigating the toxicities associated with longer-term administration of toceranib is warranted.

Biological response is similar to that reported in dogs, although this was a small cohort with advanced disease; further numbers are needed to investigate response. Toceranib therapy for oral SCC does not appear to be effective, at least in advanced disease in this cohort of cats.

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References

1 London CA, Hannah AL, Zadovoskaya R, et al. **Phase I dose-escalating study of SU11654, a small molecule receptor tyrosine kinase inhibitor, in dogs with spontaneous malignancies**. *Clin Cancer Res* 2003; 9: 2755–2768.
2 Pryer NK, Lee LB, Zadovaskaya R, et al. **Proof of target for SU11654: inhibition of KIT phosphorylation in canine mast cell tumors**. *Clin Cancer Res* 2003; 9: 5729–5734.
3 London C, Mathie T, Stingle N, et al. **Preliminary evidence for biologic activity of toceranib phosphate (Palladia) in solid tumours**. *Vet Comp Oncol* 2012; 10: 194–205.
4 Motzer RJ, Michaelson MD, Redman BG, et al. **Activity of SU11248, a multitargeted inhibitor of vascular endothelial growth factor receptor and platelet-derived growth factor receptor, in patients with metastatic renal cell carcinoma**. *J Clin Oncol* 2006; 24: 16–24.
5 London CA, Malpas PB, Wood-Follis SL, et al. **Multi-center, placebo-controlled, double-blind, randomized study of oral toceranib phosphate (SU11654), a receptor tyrosine kinase inhibitor, for the treatment of dogs with recurrent (either local or distant) mast cell tumor following surgical excision**. *Clin Cancer Res* 2009; 15: 3856–3865.
6 Bernabe LF, Portela R, Nguyen S, et al. **Evaluation of the adverse event profile and pharmacodynamics of toceranib phosphate administered to dogs with solid tumors at doses below the maximum tolerated dose**. *BMC Vet Res* 2013; 9: 190.
7 Ewer MS, Suter TM, Lenihan DJ, et al. **Cardiovascular events among 1090 cancer patients treated with sunitinib, interferon, or placebo: a comprehensive adjudicated database analysis demonstrating clinically meaningful reversibility of cardiac events**. *Eur J Cancer* 2014; 50: 2162–2170.
8 Di Lorenzo G, Autorino R, Bruni G, et al. **Cardiovascular toxicity following sunitinib therapy in metastatic renal cell carcinoma: a multicenter analysis**. *Ann Oncol* 2009; 20: 1535–1542.
9 Sella A, Hercbergs AH, Hanovich E, et al. **Does sunitinib-induced hypothyroidism play a role in the activity of sunitinib in metastatic renal cell carcinoma?** *Chemotherapy* 2012; 58: 200–205.
10 Daly M, Sheppard S, Cohen N, et al. **Safety of masitinib mesylate in healthy cats**. *J Vet Intern Med* 2011; 25: 297–302.
11 Eisenhauer EA, Therasse P, Bogaerts J, et al. **New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1)**. *Eur J Cancer* 2009; 45: 228–247.
12 Iacovelli R, Palazzo A, Procopio G, et al. **Incidence and relative risk of hepatic toxicity in patients treated with anti-angiogenic tyrosine kinase inhibitors for malignancy**. *Br J Clin Pharmacol* 2014; 77: 929–938.
13 Haas NB, Manola J, Ky B, et al. **Effects of adjuvant sorafenib and sunitinib on cardiac function in renal cell carcinoma patients without overt metastases: results from ASSURE, ECOG 2805**. *Clin Cancer Res* 2015; 15: 4048–4054.
14 Chintalgattu V, Rees ML, Culver JC, et al. **Coronary microvascular pericytes are the cellular target of sunitinib malate-induced cardiotoxicity**. *Sci Transl Med* 2013; 5: 187ra69.
15 Gundler S, Tidholm A and Haggstrom J. **Prevalence of myocardial hypertrophy in a population of asymptomatic Swedish Maine coon cats**. *Acta Vet Scand* 2008; 50: 22.
16 Riesen SC, Kovacevic A, Lombard CW, et al. **Echocardiographic screening of purebred cats: an overview from 2002 to 2005**. *Schweiz Arch Tierheilkd* 2007; 149: 73–76.
17 Paige CF, Abbott JA, Elvinger F, et al. **Prevalence of cardiomyopathy in apparently healthy cats**. *J Am Vet Med Assoc* 2009; 234: 1398–1403.