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Original Article

Combination toceranib and lomustine shows frequent high grade toxicities when used for treatment of non-resectable or recurrent mast cell tumours in dogs: A European multicentre study

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ABSTRACT

Mast cell tumours (MCTs) in dogs can present in a variety of forms. Non-resectable, recurrent or metastatic MCTs usually carry a poor prognosis and present a therapeutic challenge. Both toceranib and lomustine have shown single agent activity against MCTs in dogs. In this study, 10 dogs with advanced MCTs were enrolled prospectively and treated with toceranib (median dose 2.7 mg/kg orally every other day), lomustine (median dose 60 mg/m^2 orally every 3 weeks) and prednisolone (1 mg/kg orally every other day, alternating with toceranib). Severe adverse events (SAEs), requiring alterations in the protocol, occurred in all dogs. The objective response rate was 50%. Three dogs died or were euthanased due to SAEs and therefore enrolment of new dogs was discontinued prematurely. A long term response (>1 year) was observed in two dogs. Modifications of the protocol are required for future prospective studies.

Introduction

Mast cell tumours (MCTs) are the most common type of cutaneous tumours in dogs and comprise 11–21% of all skin tumours (Bostock, 1986; Villamil et al., 2011). The treatment of choice is wide surgical resection; adjuvant therapy, such as radiation therapy, chemotherapy and receptor tyrosine kinase inhibitors (RTKI), are recommended for improved tumour control in those cases that are not treatable by surgery. Non-resectable, recurrent and/or metastatic MCTs in dogs represent a clinical challenge and often become refractory to treatment with systemic drugs, such as vinblastine, lomustine, prednisolone and RTKI (Rassnick et al., 1999; Thamm et al., 1999, 2006; London et al., 2009; Blackwood et al., 2012; Smrkovski et al., 2013).

Toceranib and lomustine are widely used as single agents in the treatment of MCTs in dogs. Toceranib is a RTKI with activity against a wide range of split receptor tyrosine kinases. These include vascular endothelial growth factor receptor 2 (VEGFR-2), platelet-derived growth factor receptor (PDGFR)-α/ß, stem cell factor receptor c-Kit, fms-related tyrosine kinase 3 (Flt-3) and colony stimulating factor receptor 1 (CSFR1) (Liao et al., 2002; London et al., 2003). Toceranib is approved by the European Medicine Agency (EMA) and the USA Food and Drug Administration (FDA) for the treatment of non-resectable, Patnaik grade II or III (Patnaik et al., 1983), recurrent, cutaneous mast cell tumours in dogs. The most commonly observed adverse events (AEs) related to treatment with toceranib are neutropenia and gastrointestinal (GI) signs (e.g. anorexia, diarrhoea and vomiting), with grade III or IV GI AEs observed in 2.3–9.2% of cases (London et al., 2003). Other AEs, such as proteinuria, lethargy and muscle pain, have also been described (London et al., 2003; Gore et al., 2009). The objective response rate (ORR) in toceranib-treated dogs with recurrent (either local or distant) MCTs following surgical excision was 37.2% in one study (London et al., 2009).

Lomustine, also known as 1-(2-chloroethyl)-3-cyclohexyl-1-nitrosourea (CCNU), is a cell cycle non-specific DNA alkylating

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agent used for the treatment of a variety of neoplastic conditions in veterinary medicine (Moore et al., 1999; Kristal et al., 2004; Jung et al., 2006; Risbon et al., 2006; Williams et al., 2006; Saba et al., 2007; Cooper et al., 2009; Rassnick et al., 2010a,b). The most commonly observed AEs associated with lomustine include bone marrow suppression and hepatotoxicity, with GI side effects reported rarely and mainly in association with sepsis (Moore et al., 1999; Rassnick et al., 1999; Kristal et al., 2004). Response rates to treatment with single agent lomustine in dogs with MCTs are 1–42% (Rassnick et al., 1999; Vail at al., 2012), while the reported response rate to treatment with oral prednisolone alone is 20% (McCaw et al., 1994).

The aim of this prospective study was to assess the ORR, progression-free interval (PFI) and toxicity profile of a combined lomustine-toceranib-prednisolone protocol in dogs with high-grade (Patnaik grade II/III) non-resectable and/or recurrent, or metastatic, MCTs. The hypothesis was that a combination protocol with lomustine, toceranib and prednisolone would be well tolerated, since these are drugs with known single agent activity that lack overlapping dose limiting toxicities. It was hypothesised that the protocol would induce responses in >20% of non-resectable and/or recurrent high grade, or metastatic, MCTs in dogs.

Materials and methods

This prospective European multicentre study was a collaboration of seven universities and veterinary oncology centres across Europe (University of Edinburgh, Hospital for Small Animals, United Kingdom; Veterinary Oncology Referral Centre, Animal Hospital Zeeuws-Vlaanderen, Terneuzen, The Netherlands; Tierklinik Hofheim, Hofheim, Germany; Centre Micen Vet, Créteil, France; University of Turin, Dipartimento di Scienze Veterinarie, Grugliasco, Torino, Italy; Animal Health Trust, Suffolk, United Kingdom, and the Clinic of Small Animal Medicine, Ludwig-Maximilians-Universität, Munich, Germany). Dogs were enrolled in the study from October 2012 to January 2013.

Selection of subjects

Client owned dogs with measurable primary or recurrent, non-resectable and/or metastatic Patnaik grade II/III MCTs diagnosed on histopathology, with a minimal estimated life expectancy of 8 weeks without treatment, were eligible to be included the study. A written informed consent form was signed by the owners prior to enrolment. Routine MCT staging was performed, including clinical examination, regional lymph node cytology, abdominal ultrasound with or without liver and spleen cytology, thoracic radiography, haematology, serum biochemistry and urinalysis. Evaluation of lungs, liver, spleen and lymph nodes using computed tomography (CT) was also allowed. Pre-treatment with other chemotherapeutic agents within 30 days prior to enrolment or curative intent local treatment was not allowed. Treatment with antihistamines and GI protectants was allowed, but not routinely recorded.

Treatment protocol

The planned doses were 70 mg/m^2 lomustine phosphate orally every 3 weeks and 2.7 mg/kg toceranib (Palladia, Zoetis) orally every other day, starting a day after lomustine, for at least six cycles, unless progressive disease or severe adverse events (SAEs) were reported, with the dose adjusted to the nearest dose that could be administered using available whole capsules of lomustine or tablets of toceranib. The planned dose of prednisolone was 1 mg/kg, administered orally on days alternating with toceranib. Total treatment time was planned to be 6 months or until detection of progressive disease. All target lesions were routinely measured using calipers and digitally photographed on the day of administration of lomustine.

Haematology was performed immediately prior to each dose of lomustine and 1 week after administration of lomustine. Serum biochemistry was repeated every 3 weeks also immediately prior to the planned administration of lomustine. The dose of lomustine was delayed if the neutrophil count was $<2.0 \times 10^9$/L or the platelet count was $<100 \times 10^9$/L; in these cases, a 10–15% dose reduction was applied at subsequent administration. When SAEs were

Table 1
Treatment details of dogs included in the trial.

	Category	*n*
Lomustine	Number of doses (range)	29 (1–6)
	Dose in mg/m^2 (range)	60 (50–88.9)
Toceranib	Dose in mg/kg (range)	2.70 (2.50–2.79)
	Duration (weeks)	11.5 (5–23)
DLTs	Total number	26
	Median/dog (range)	2 (1–6)
Neutropenia (Grade III and IV)	Total number	15
	Median/dog (range)	1 (1–4)
Prophylactic antibiotics	Total number	6
Pyrexia	Total number	2
GI toxicity (grade III or IV)	Total number	9
	Nausea	1
	Vomiting	6
	Diarrhoea	2
Other toxicities	Pancreatitis (grade IV)	1
	Hepatotoxicity (grade IV)	1
Drug withdrawal periods (toceranib)	Total number	9
	Median/dog (range)	2 (1–4)
	Median duration in weeks (range)	1 (1–2)
Response	Complete remission (CR)	3
	Partial remission (PR)	2
	Stable disease (SD)	3
	Progressive disease (PD)	2
	Overall response rate (OOR)	50%

MCT, mast cell tumour; DLT, dose limiting toxicity; GI, gastrointestinal.