THE MANY CLINICAL USES OF PALLADIA

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Toceranib phosphate/PALLADIA® (Zoetis)

Canine

Toceranib phosphate (Palladia®) is a multireceptor tyrosine kinase (RTK) inhibitor approved by the FDA Center for Veterinary Medicine in 2009 for the treatment of dogs with recurrent cutaneous Patnaik grade II or III mast cell tumors. By inhibiting several members of the split-kinase family of RTKs, including vascular endothelial growth factor receptor-2 (VEGFR-2), platelet-derived growth factor receptor-β (PDGFR-β), and Kit/stem cell factor receptor (SCFR), toceranib has both an antiangiogenic as well as direct antitumor role in treating canine mast cell tumors.

Palladia has been demonstrated to be effective and well-tolerated in a prospective, placebo-controlled, multi-center field study in dogs with mast cell tumor.[1] There are a number of recent publications to review that help to further define the best clinical use of this powerful therapeutic in various carcinomas and sarcomas in dogs.

A. Pulse-dosed Palladia + lomustine for nonresectable canine mast cell tumor (MCT)
Lomustine at a dosage of 50 mg/m^2 once every 3 weeks combined with pulse-dosed Palladia was well-tolerated. The objective response rate of 46% for this protocol is comparable to what previously has been reported for single-agent protocols, but considerably higher than that reported with single-agent lomustine. Combining pulse-administered Palladia with lomustine may be a reasonable treatment option for dogs with unresectable or metastatic MCT.[2]

B. Maintenance Palladia following doxorubicin-based chemotherapy for canine splenic hemangiosarcoma (HSA)
Results of this study indicate that use of Palladia following doxorubicin chemotherapy does not improve either DFI or ST in dogs with stage I or II HSA compared to previously published reports of adjuvant chemotherapy for splenic HSA.[3]

C. Impact of Palladia/piroxicam/cyclophosphamide maintenance therapy on canine osteosarcoma (OSA)
The addition of Palladia to metronomic piroxicam/cyclophosphamide therapy following amputation and carboplatin chemotherapy did not improve median DFI, OS or the 1-year survival rate in dogs with OSA.[4]

D. Evaluation of Palladia administered to dogs with solid tumors at doses below the maximum tolerated dose
Palladia administered at doses between 2.4-2.9 mg/kg PO q48h resulted in an average 6–8 hr plasma concentration ranging from 100–120 ng/ml, well above the 40 ng/ml concentration associated with target inhibition. The lower doses of Palladia used in this study were associated with a substantially reduced adverse event profile compared to the established label dose of 3.25 mg/kg q48h.[5]

E. Continuous Palladia dosing in combination with cytotoxic chemotherapeutics
Studies evaluating the use of continuous Palladia dosing in combination with vinblastine,[6] CCNU,[7] and doxorubicin[8] have been described. These reports provide initial information on how to potentially utilize Palladia concurrently with other anti-cancer agents.

Feline

Although approved for use in dogs, initial safety and toxicokinetic data for cats has been previously outlined.[9] An abundance of clinical data reporting on the use of Palladia in cats has been published this year (Table 1). Key findings of each study and the overall clinical use of Palladia in cats will be summarized during the presentation.

Table 1: Recent data regarding the use of toceranib in cats and specific adverse events.

	Berger et al[10]	Wiles et al[11]	Holtermann, Kiupel, and Hirschberger[12]	Olmstead et al[13]	Merrick et al[14]	Harper and Blackwood[15]
E-Pub Date	N/A	11 Jan 2016	14 Jan 2016	7 Mar 2016	4 Apr 2016	18 Apr 2016
Disease evaluated	Mast cell tumor	Oral squamous cell carcinoma	Injection site sarcoma	Oral squamous cell carcinoma	Spontaneous malignancies	Spontaneous malignancies
Number of cats	53	23	18	35	55	14
Dose	2.5mg/kg	2.52mg/kg	3.25mg/kg	2.75mg/kg	2.7mg/kg	2.78mg/kg
Most common AE category	Gastrointestinal (Inappetence)	Gastrointestinal (Anorexia)	Gastrointestinal (Anorexia)	Gastrointestinal (Vomiting)	Hematologic (Thrombocytopenia)	Hematologic (Neutropenia)
Most common AE % (n)	22 (n=12)	70 (n=16)	56 (n=10)	6 (n=2)	16 (n=9)	29 (n=4)
Incr. ALT VCOG grade (1/2/3/4)	4 2/1/1/0	2 1/0/0/1	4 0/0/0/4	1 0/0/0/1	4 2/0/1/1	2 0/0/0/2
Incr. ALP	1	1	1	0	0	0
VCOG grade (1/2/3/4)	0/1/0/0	1/0/0/0	0/1/0/0	-	-	-

AE = adverse event; ALT = alanine aminotransferase; ALP = alkaline phosphatase

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