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Palladia™ (toceranib phosphate) - What do you need to know?
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Brenda Phillips, DVM, ACVIM (Oncology)

Palladia is produced by Pfizer and is the first drug approved by the FDA to treat cancer in animals. Palladia is a small molecule that inhibits multiple receptor tyrosine kinases. Its primary mechanism of action is insertion into ATP binding pockets of these receptors, blocking activation and resulting in prevention of cell division and proliferation.

Palladia specifically blocks activity of platelet-derived growth factor receptor-beta (PDGFR- β), vascular endothelial growth factor receptor-2 (VEGFR-2), and stem cell factor receptor (Kit). Palladia treatment has been shown to induce cell cycle arrest and subsequent cell death in tumor cell lines expressing activating mutations in c-kit. Further, Palladia has anti-angiogenic properties. In clinical trials including 145 dogs with measurable, cutaneous mast cell tumor of grade II or III histology, w/ or w/o lymph node metastasis, 42.8% of tumors responded with a size reduction of at least 30%. Patients with c-kit mutated tumors were more likely to have a measurable tumor response, though c-kit mutation testing is not required prior to treatment with Palladia as non-mutated tumors may also respond.

Another c-kit inhibitor has been licensed in Europe to treat canine mast cell tumors. This drug, masitinib, is produced by AB Science and they are seeking FDA approval to market this drug in the United States. This drug has been associated with long-term control of canine mast cell tumors, with the best results seen in dogs with c-kit mutated mast cell tumors.

Most mast cell tumors in dogs are cured following surgical excision. However, multifocal, locally recurrent, or high grade mast cell tumors present a therapeutic challenge and may compromise patient survival. Palladia was approved to treat dogs with recurrent grade II or III mast cell tumors +/- regional lymph node involvement. This drug appears most effective and is used most safely when administered in the setting of minimal tumor burden. It may therefore be most useful after surgery and/or chemotherapy have been used to achieve minimal tumor burden.



Palladia is considered to have a narrow margin of safety. Similar to use of cytotoxic chemotherapeutic agents, neutropenia or gastrointestinal sequelae may cause significant morbidity or become life-threatening. Therefore, it is imperative that regular monitoring for GI complications and of CBC and biochemical values is performed when Palladia is used, and careful adherence to label recommendations for dosing adjustments in response to identified toxicity is critical. I advise my clients and staff to observe safety protocols as used for cytotoxic chemotherapy when Palladia is utilized.

Based on mechanism of action and results from open-label trial, Palladia should prove useful in the future to treat non-mast cell tumor neoplastic conditions. It will may prove useful as a chronic chemopreventive strategy to delay or prevent “waves” of *de novo* multifocal dermal mast cell tumors. Additionally, receptor tyrosine kinase inhibitors may prove effective to treat non-neoplastic conditions. For example, masitinib is being evaluated as a treatment for canine atopy. At this time, it is considered a welcome, additional therapy for treatment of biologically aggressive canine mast cell tumors.

If you have questions about receptor tyrosine kinase inhibitors, please do not hesitate to call Dr. Brenda Phillips or Dr. Blaise Burke at 858-875-7575.

