
PalladiaTM
toceranib phosphate

Practical Case Management

Based on the clinical experience of
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Appropriate MCT Case Selection is Important

- Debulking/cytoreduction of tumor(s) remains a critical component of therapy prior to initiating PALLADIA
 - Surgery (potentially repeat surgery for complete margins)
 - Cytotoxic chemotherapeutics (including prednisone)
 - Radiation therapy
- In dogs with bulky MCT, consider supportive care prior to initiating PALLADIA therapy
 - 7 to 10 days prior to PALLADIA therapy
 - H1 blocker (e.g., diphenhydramine)
 - H2 blocker (e.g., famotidine) or proton-pump inhibitor (e.g., omeprazole)
 - GI protectants (e.g., sucralfate)
 - Prednisone
- Stabilize dogs that are in poor condition/status prior to initiating PALLADIA therapy
 - See list above
 - Other supportive measures as clinically indicated

Appropriate MCT Case Selection is Important

- Reduction of tumor volume remains a critical component of therapy prior to initiating PALLADIA
 - Surgery (potentially repeat surgery for complete margins)
 - Cytotoxic chemotherapeutics (including Prednisone)
 - Radiation therapy
- Grade II MCT
 - High-risk (recurrent, metastatic, or negative prognostic factors such as high mitotic index or recent rapid growth)
 - Following appropriate standard of care (4 to 8 cycles of vinblastine/prednisone)
- Grade III MCT
 - All grade III MCTs following appropriate standard of care:
 - 4 to 8 cycles of vinblastine/prednisone
 - Radiation therapy when appropriate for incompletely excised or non-resectable tumors
- Referral to / consultation with oncology specialist should be considered prior to initiation of therapy

Most AEs Seen With PALLADIA Are Mild to Moderate and Are Generally Manageable

- All multireceptor kinase inhibitors have AEs
- The spectrum of AEs is often dictated by the array of receptor/target inhibition
- AEs observed are often similar to those that occur with other systemic therapies, such as chemotherapy
- AEs can be serious, but most are mild to moderate and are generally manageable with appropriate supportive care or dose/schedule modification
- Life-threatening AEs are rare with PALLADIA, although early recognition of potential problems is critical

Several Factors Are Likely to Influence the Spectrum and Severity of AEs

- Stage of disease
 - Dogs with more advanced disease generally have a lower performance score, which could potentially influence the severity of AEs; this has been shown to be the case in humans treated with multitargeted therapies
- Type of cancer
 - Dogs with macroscopic MCT are known to have high circulating levels of histamine, which can predispose to GI ulceration and other GI AEs; these could be compounded by PALLADIA therapy
- Pre-existing conditions
 - Liver disease, renal disease, and cardiac disease can all influence performance scores, and these may also impact drug metabolism/elimination, thereby compounding AEs
- Concomitant medications
 - Certain drugs may exacerbate GI AEs or impair drug metabolism

Monitoring and Rechecks Are Recommended

Visit	CBC	Serum chemistry	Hemoccult	Urinalysis	Weight
Baseline	✓	✓	✓	✓	✓
Week 1	✓				✓
Week 2	✓		✓		✓
Week 3	✓				✓
Week 4	✓	✓	✓	✓	✓
Week 5	✓				✓
Week 6	✓				✓
Week 12	✓	✓	✓	✓	✓
Every 6 weeks	✓	✓	✓*		✓*

*Test hemoccult and weight only if health concerns remain.

Active Prevention of GI AEs Is Recommended

- H1 blocker (diphenhydramine)
- H2 blocker (famotidine)
- PPI (omeprazole)
- Antiemetic (maropitant citrate, ondansetron, metoclopramide)
- Adjust agents and dose based on patient response and disease characteristics

GI Toxicities Are Generally Manageable, Especially With Early Intervention

- Treatment should be initiated at the first evidence of clinical signs
- Therapies to consider in addition to preventive medications:
 - Metronidazole
 - Loperamide
 - Sucralfate
- If GI signs do not respond to therapy, or are severe, a treatment break should be initiated followed by an alteration in drug schedule and/or dose
- If melena or hematochezia is noticed, PALLADIA should be stopped immediately and supportive care instituted (omeprazole, sucralfate, antibiotics, or fluids, as clinically indicated)

Management of Musculoskeletal AEs (Cramping/Lameness) With PALLADIA

- Institute treatment break if significant lameness is present; if lameness is mild, you may add concomitant medications
- Tramadol may be useful for pain/discomfort
- NSAID therapy tends to work well but must be used carefully with respect to GI AEs/GI ulceration if using in concert with PALLADIA; consider using on PALLADIA “off” days
- Lameness is usually not severe and does not seem to be a recurrent problem when therapy is reinitiated following treatment break

Clinically Relevant Neutropenia Does Not Seem to Occur With PALLADIA

- Grade 3 or 4 neutropenia occurred in only 2 out of 145 dogs treated with PALLADIA in the clinical field study (blinded plus open-label phase) and was not associated with active infection
 - In the rare case of severe neutropenia, initiate treatment break
- No grade 3 or 4 neutropenia was noted in the phase 1 study
- Given the lack of clinical effect, no treatment for neutropenia (ie, granulocyte colony-stimulating factor) is recommended

Dose Adjustments Minimized Toxicity While Maintaining Efficacy During the Clinical Field Study

- In the clinical field study, the PALLADIA dose was reduced in 0.5 mg/kg decrements to a minimum of 2.2 mg/kg EOD, or interrupted, if needed, to manage AEs
- Flexible dosing can be used to individualize care

Total number of dogs		Dose reduction		Treatment Break		
		1	2	1	2	3
PALLADIA	87	18.4%	1.1%	40.2%	6.9%	1.1%
Placebo	64	6.3%	0.0%	9.4%	1.6%	0.0%

General Recommendations for Dose or Schedule Modifications

- For dogs with minor AEs, consider reducing dose slightly or modifying their schedule to Monday, Wednesday, and Friday, with the weekend off
- Consider adding supportive care, as previously described, including antidiarrheal drugs (loperamide), antiemetics (maropitant citrate, metoclopramide), and GI protectants (famotidine, omeprazole)
- If AEs persist despite modifying dosing schedule, consider an every-third-day dosing schedule
 - This may be necessary for dogs with other underlying medical issues

Case Management Summary

- AEs with PALLADIA are similar to those that occur with standard chemotherapeutics
- AEs are likely to be compounded by the type of cancer, disease stage, and performance status of the patient
- Early recognition of AEs and appropriate intervention are critical if patients are to receive PALLADIA long term
- Long-term PALLADIA administration with an excellent quality of life is possible for many patients

Client Education is Critical to Successful Use of PALLADIA

- Important that client clearly understands potential side effects and clinical signs
 - Enables early recognition and intervention if dog experiences side effects
- Client educational resources available:
 - Client Information Sheet (see label and DVM website)
 - Pet Discharge Instructions (see DVM website, customizable)
- Ensure technical staff is familiar with general PALLADIA information and common client questions so all team members are communicating same information
 - Educational webinars (see DVM website)
 - FAQs and Glossary of Terms (see DVM website)
 - Client Information Sheet (see label and DVM website)
 - PALLADIA Product Overview (included in initial product shipment)

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PALLADIA Label Safety Review

5 Deaths Were Possibly Related to PALLADIA

- Vascular thrombosis with disseminated intravascular coagulopathy (DIC) and pancreatitis
- Vascular dysfunction, including pulmonary thromboembolism (postoperative)
- Multiorgan failure associated with vasculitis and thrombosis
- Vasculitis with DIC
- Gastric perforation
 - Dog achieved CR, with no evidence of MCT at necropsy
 - Total duration of PALLADIA treatment was 221 days (99 days after CR)
- Treatment durations for the 5 on-study deaths ranged from 18 days to 221 days

PALLADIA Label Warnings

- Vascular dysfunction
 - PALLADIA may cause vascular dysfunction that can lead to edema and thromboembolism, including pulmonary thromboembolism
 - Discontinue drug until clinical signs and clinical pathology have normalized. To ensure vasculature homeostasis, wait ≥ 3 days after drug cessation before performing surgery
- GI complications
 - Serious, and sometimes fatal, GI complications, including GI perforation, have occurred rarely in dogs treated with PALLADIA
 - If GI ulceration is suspected, stop drug administration and treat appropriately

User Safety and Handling

- PALLADIA was specifically designed for, and tested in, dogs
- Not for use in humans
 - Keep children away from PALLADIA and from feces, urine, or vomit of treated dogs
- Avoid exposure to drug
 - Wash hands with soap and water after administration
 - Wear protective gloves to prevent direct contact with feces, urine, vomit, and broken/moistened tablets
 - Place all waste materials in plastic bag and seal for general disposal
 - Do not split tablets
 - In case of accidental ingestion, seek medical advice immediately; GI discomfort may occur
- Pregnant women, women who may become pregnant, or nursing mothers should pay special attention to handling precautions as PALLADIA belongs to a class of agents that may cause harm to the unborn baby

Summary

- Most common adverse events (AEs) reported with PALLADIA involve the GI tract
 - Early recognition and intervention is crucial to preventing more serious AEs
- Less commonly observed AEs include lameness and bone marrow suppression
- PALLADIA can cause clinical signs similar to those seen with aggressive MCT so it is imperative to stop drug and re-evaluate patient when signs are observed
- AEs can often be managed with temporary discontinuation of drug and/or dose reductions
- Dogs in poor health and/or with bulky MCT prior to starting PALLADIA are at a great risk for developing AEs
 - Treatments to reduce tumor volume and improve patient's health status are recommended prior to initiating PALLADIA therapy (i.e., surgery, radiation therapy, chemotherapy, supportive medications)
 - Referral to / consultation with oncology specialist prior to treatment should be considered
- Owner education is necessary for successful use of PALLADIA
 - Owners must never become complacent during PALLADIA therapy