STELFONTA® for MAST CELL TUMORS IN 2023: HOW TO GET STARTED AND WHAT WE HAVE LEARNED SO FAR

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STELFONTA® INTRODUCTION

STELFONTA® (tigilanol tiglate injection) is approved by the FDA as a prescription intratumoral injection indicated for the treatment of nonmetastatic cutaneous mast cell tumors and nonmetastatic subcutaneous mast cell tumors located at or distal to the elbow or the hock.[3] Tigilanol tiglate is part of a novel small molecule class of drugs called epoxy-tiglianes. It is isolated from the seed of *Fontainea picrosperma* (blushwood tree).[1,2] Its unique mode of action sets it apart from other local treatment therapies.

STELFONTA® MODE OF ACTION[1]

The intratumoral injection of STELFONTA has three interrelated effects responsible for its anti-tumor properties. The first effect is oncolysis of tumor cells that come into direct contact with the drug. This occurs predominantly along the needle tracks during fanning of the drug within the tumor. This effect is noted within hours and is the effect of disruption of mitochondria and tumor cell membranes leading to necrosis. Second, the drug activates protein kinase C (PKC) β-II isoforms in the tumor endothelial cells. This affinity for β-II isoforms is highly specific and results in increased vascular permeability and loss of tumor vascular integrity. This results in the treated tumor having a bruised appearance within hours of the injection. Thirdly, STELFONTA activates a PKC signaling cascade throughout the mass resulting in an acute inflammatory response. The tumor and immediate surroundings develop swelling and erythema. The inflammatory response usually resolves in 2-4 days. Importantly, this inflammation actively leads to restriction of blood and oxygen supply to the tumor and recruitment of innate immune cells which target the tumor mass. These effects have a cumulative effect of necrosis of the tumor mass followed by slough of the tumor within 3-14 days. (Figure 1)

The induction of an innate immune response plays an antimicrobial role and initiates downstream cytokine signaling that contributes to subsequent initiation of wound healing at the site of necrotic tumor slough. STELFONTA has demonstrated direct effects on keratinocyte and fibroblast function via production of cytokines and chemokines that are associated with promotion of wound healing at the treatment site. Complete healing of the wound following tumor necrosis and slough occurs in most patients within 4-6 weeks.

STELFONTA® CLINICAL SAFETY AND EFFICACY[4]

Study Design: A clinical trial was performed in the United States to evaluate the effectiveness and safety of STELFONTA in dogs in a typical clinical environment. There were 123 client-owned dogs enrolled in a multi-center, randomized, untreated controlled, investigator and owner blinded study. Dogs were screened to have non-metastatic cutaneous mast cell tumor anywhere on the body or non-metastatic subcutaneous mast cell tumor located at or distal to the elbow or hock. The tumor could not have significant ulceration as this may have led to leakage of the drug and resultant decrease in efficacy. Patients were excluded for systemic signs of mast cell tumor (vomiting, diarrhea, inappetence) or previous treatment (radiotherapy, surgery, or biopsy). Patients were not allowed to have been treated with nonsteroidal anti-inflammatory drugs within 7 days or immunosuppressive doses of corticosteroids or anti-atopic medication within 14 days. All dogs received concomitant medications consisting of a steroid (prednisone/prednisolone) at anti-inflammatory dose, an H1 antagonist (diphenhydramine) and an H2 antagonist (famotidine). (Figure 2) Patients were limited to a maximum treatable tumor volume of 10 cm^3 and the dose could not exceed 0.25 mL/kg or 5 mL per dog regardless of the tumor volume or body weight of the patient.[3] The enrolled dogs were randomized in a 2:1 ratio to receive a single injection of tigilanol tiglate or

evaluated as part of the untreated control group. There were several reassessments; however, the primary assessment for efficacy was performed at Day 28. Any patients randomized to the treatment group that did not achieve a complete response at Day 28 had the option to receive a second treatment. In addition, any patients in the untreated control group that were assessed at Day 28 that did not have a complete response could crossover and receive tigilanol tiglate treatment.
Study Results – Efficacy: A single injection of tigilanol tiglate resulted in a 75% (60/80) complete response. The objective tumor response (complete response and partial response) was 80% (64/80). Eighteen STELFONTA treated dogs that had not achieved a CR received a second treatment increasing the complete response rate to 88% after one or two treatments.
Study Results – Safety: A second important aspect of this study was safety. Of the reported adverse events, 94% were grade 1 or 2, considered mild to moderate with 61% expected as part of the mode of action of the drug. These included wound formation at the treatment site, tumor and injection site pain, lameness in the treated limb, injection site bruising, erythema and edema, and regional lymph node enlargement.
Management and Healing at the Treatment Site: There were 117 dogs that received a single treatment. Only 5/117 (4%) received active wound management which included one bandaged, one flushed with saline to decrease odor, two wore Elizabethan collars and one received antibiotics for a wound cultured positive for bacteria. Complete wound healing occurred in 57% of patients by Day 28, 78% by Day 42, and 96% of cases by Day 84.

STELFONTA® CASE SELECTION
STELFONTA case selection is important for success. The largest temptation is to use STELFONTA for excessively large tumors and those tumors that have failed multiple treatments. There are several factors for veterinarians to consider in all cases and this is no different when treating patients with STELFONTA. There are tumor, patient, and owner factors that go into each patient's treatment recommendations and decisions.Like surgery, there are numerous tumor factors to consider with STELFONTA injection and clinicians will gain more insight with use and experience. Patients are never a one size fits all approach. Some of the factors include tumor location, ulceration, tumor volume, proximity to functional structures, mucocutaneous junctions, sensitivity, and local infiltration. Each patient can present with a variety of different factors unrelated to the tumor that may make them a suitable or unsuitable candidate for certain treatment recommendations. These may include concurrent diseases, temperament, age, and breed-associated risks. I recommend cytologic grading be done by a cytologist for STELFONTA cases. In addition, we must partner with owners to make the best possible recommendations and decisions for each patient. Owner considerations may be fear of the unknown regarding the treatment or compliance in follow up care. Owner education about the STELFONTA journey is critical. Client information sheets can be found on the Virbac website for veterinarians. In addition, I strongly encourage the owner to visit the STELFONTA website and watch my YouTube vlogs (see below).

CYTOLOGIC GRADING
MCT can be graded with cytology. Advantages include aspirates can be done more quickly, inexpensively, and less invasively than biopsy. There are a few recent publications that show high sensitivity and specificity. In the Camus study of 152 dogs, a cytologic grading scheme was created based on correlation with histologic grade. A MCT was high grade if it was poorly granulated or had at least 2 of 4 findings: mitotic figures, binucleated or multinucleated cells, nuclear pleomorphism, or >50% anisokaryosis. The cytologic grading scheme had 88% sensitivity and 94% specificity relative to histologic grading. Dogs with histologic and cytologic high grade MCTs were 39 times and 25 times more likely to die within the 2-year follow-up period, respectively, than dogs with low grade MCTs. High tumor grade was associated with increased probability of additional tumors or tumor regrowth. This study concluded that cytologic grade is a useful predictor for treatment planning and

prognostication. I recommend you request this from your cytologist, especially when treating with STELFONTA.

INDICATIONS

STELFONTA® (tigilanol tiglate injection) is indicated for the treatment of non-metastatic canine mast cell tumors. Tumor volume should not exceed 10 cm^3. For cutaneous MCT, the MCT can be located anywhere on the body. For subcutaneous MCT, the MCT must be located at or distal to the elbow or the hock. STELFONTA should not be injected into *subcutaneous* mast cell tumors located above the elbow or hock (e.g., on the body, head, or neck) as this may result in accumulation of necrotic debris in the subcutaneous space increasing the risk of systemic adverse reactions, including death, from mast cell degranulation.

STELFONTA® FOUR STAGES OF TREATMENT

It is best to think of STELFONTA treatment in four stages – concomitant medications, STELFONTA injection, tumor destruction, and tumor site healing.

Stage 1 - Concomitant medications – pretreatment:

- This is an essential element of the protocol directed at decreasing the risk associated with mast cell tumor degranulation.
- See Figure 2 for recommended dosing.
    - Steroids must start 2 days before STELFONTA treatment day as directed, though patients can start steroids before this day
    - Famotidine and diphenhydramine must be given the morning of treatment day by owners. (I now start all 3 essential medications at least 2 days before.)
- While all patients do not need analgesia, consider preemptive pain management as STELFONTA injection results in an acute local inflammatory response followed by tumor necrosis. I recommend proactive pain management for STELFONTA patients especially the limb locations. My protocol is to have clients start gabapentin the day of treatment when they get home @10 mg/kg PO BID and increase to TID if the dog is painful. For limb locations, be sure to advise clients about potential lameness and edema. Opioids can be added if necessary. NSAIDs must be avoided while the dogs are on steroids.

Stage 2 - STELFONTA injection:

- Important to confirm with the owner that the concomitant medication schedule has been followed.
- Accurate tumor measurement and dosing leads to better efficacy.
- Tumor Volume (cm^3) = 0.5 x [length (cm) x width (cm) x height (cm)]
- Tumor Volume should not exceed 10 cm^3
- Dose Volume (mL) = Tumor Volume (cm^3) x 0.5mL
- The formulation of STELFONTA is 1 mg per mL. The minimum dose is 0.1 mL, and the maximum dose is 0.25mL/kg body weight given in a maximum 5 mL dose regardless of tumor volume or body weight.
- While sedation is not required, it may be considered if the location of the tumor is in a sensitive location or as the patient's temperament dictates.
- For safety, use a Luer-lock syringe for injection to avoid leakage and potential exposure. Always wear recommended personal protective equipment (PPE) consisting of disposable gloves, protective eyewear, and a lab coat or gown.
- A 23-gauge needle is recommended.
- Disseminate the drug throughout the tumor in a fanning motion and minimize to a single injection site to prevent leakage of the drug from previous sites.
- Each vial contains 2 mL and is single use. You may need more than one vial depending on tumor volume.

Stage 3 – Tumor Destruction:

- Avoid bandaging the treatment site as it may restrict blood flow or compromise healing.
- Swelling, bruising and redness are all part of the process; wound formation is part of the mode of action and demonstrates efficacy.
- Some discharge and odor from the treatment site is expected and normal. The site can be cleaned with warm water or saline as necessary. Wear disposable gloves when cleaning the site.
- Necrotic slough is normal. If the necrotic tissue or scab is still present 14 days after the treatment, it can be removed but removal is not necessary unless the patient is not able to access the site. It is advised to NOT remove it if it is adherent or attached to underlying tissue.

Stage 4 – Tumor Site Healing:

- In most patients, healthy well-developed granulation tissue is present when the necrotic tumor sloughs.
- Wounds typically heal by second intention with no intervention required. Only one patient in the clinical study had active bandage wound management.
- Elizabethan collars are usually not necessary.
- No restriction on activity of the dog is required. Pets can be bathed or swim with extra care taken with the treatment site.

RETREATMENT

Wait 28 days to assess response, and aspirate to confirm if there is residual MCT. If MCT is confirmed with cytology, treatment can be repeated. Concomitant medications must be repeated with the same schedule and dose.

IMPORTANT SAFETY INFORMATION:

Accidental self-injection of STELFONTA® (tigilanol tiglate injection) may cause severe wound formation. To decrease the risk of accidental self-injection, sedation of the dog may be necessary. In dogs, do not inject STELFONTA into subcutaneous mast cell tumors located above the elbow or hock. Formation of wounds, possibly extensive, is an intended and likely response to treatment with STELFONTA along with associated swelling, bruising and pain; these wounds are expected to heal. Appropriate pre- and post-treatment medications must be given, including a corticosteroid plus blocking agents for both H1 and H2 receptors, to decrease the potential for severe systemic adverse reactions, including death, from mast cell degranulation.
For full prescribing information, contact VIRBAC at 1-800-338-3659 or visit https://vet-us.virbac.com/stelfonta.

VETERINARY AND PET OWNER FEEDBACK

In a recent survey of clinics using STELFONTA, 29 veterinarian evaluations and 30 pet owner evaluations were completed with a total of 44 patients.[6] This was an experience trial designed to gauge veterinarians' and pet owners' experience with and impression of STELFONTA® (tigilanol tiglate injection). treatment. Veterinarians and pet owners were asked to report their overall treatment experience, observations during the healing process, satisfaction with treatment, support materials, tumor size/location and overall resolution from treatment. Veterinarians were also specifically asked about their willingness to recommend to colleagues. Study patients ranged from 1-15 years in age and were nearly 2:1 female: male. There were a wide range of breeds included with Boxers, Labradors/Retrievers/mixes, Pitbull/mix, Pug/mix being the most represented breeds. The trunk was the most common location of tumor treated, and tumor volume of the MCT ranged from 0.1 to 10 cm^3. Over half of the patients were sedated for treatment (55%). In 72% of patients, the tumor was destroyed by day 25-31 at recheck. 69% of the veterinarians reported the tumor was mostly/completely healed by Day 25-31 recheck. All patients received one injection except for one patient that received two. 84% of pet owners were satisfied with the healing process, and 86% of

veterinarians were satisfied with the overall treatment experience. 93% of veterinarians found STELFONTA easy to administer, and 100% of surveyed veterinarians will continue to use STELFONTA and recommend it to their peers. In addition, many pet owners and veterinarians are posting and discussing STELFONTA online using social media sites, even creating pages for their pets' STELFONTA journeys. There is a popular Facebook group called STELFONTA Injection for mast cell tumors in dogs. I often recommend this one to my clients who are considering or who have chosen to treat with STELFONTA.

ONLINE RESOUCRES:

- More veterinary information can be found at https://vet-us.virbac.com/stelfonta
- For pet owners https://stelfonta.com/
- 7 Things You Need to Know about Stelfonta for Mast Cell Tumors: VLOG 130 https://youtu.be/32Sq2yD_oEM
- Where'd The Tumor Go? New FDA Treatment Works For Mast Cell Tumors VLOG 131 https://youtu.be/jAb3F1g0dw0
- Stelfonta in Action for Mast Cell Tumors in Dogs Vlog 132 https://youtu.be/kNeTEd9o520

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2. Grant EL, et al. *Floral and reproductive biology of the medicinally significant rainforest tree, Fontainea picrosperma (Euphorbiaceae)* Industrial Crops & Products 108 (2017) 416-422.
3. Food and Drug Administration Center for Veterinary Medicine, Package Insert, 2020.
4. De Ridder TR, Campbell JE, Burke-Schwarz C, et al. Randomized controlled clinical study evaluating the efficacy and safety of intratumoral treatment of canine mast cell tumors with tigilanol tiglate (EBC-46). J Vet Intern Med. 2020;1–15. https://doi.org/10.1111/jvim.15806
5. Camus MS et al. Vet Pathol. 2016 Nov;53(6):1117-1123. doi: 10.1177/0300985816638721.
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Figure 1: STELFONTA mode of action

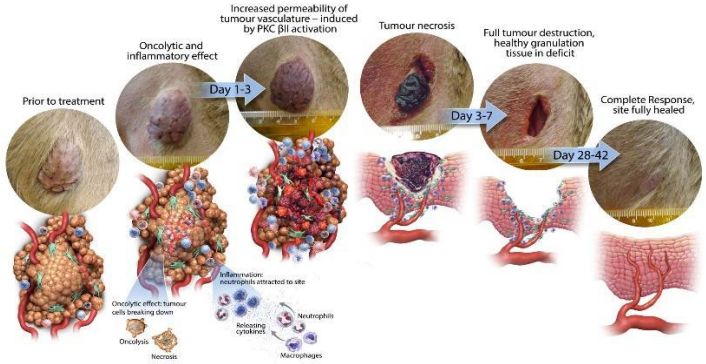

Figure 2: STELFONTA Concomitant medications