

Treatment of High-Risk Mast Cell Tumors in Dogs

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In the Literature

Miller RL, Van Lelyveld S, Warland J, Dobson JM, Foale RD. A retrospective review of treatment and response of high-risk mast cell tumours in dogs. *Vet Comp Oncol*. 2016;14(4):361-370.

FROM THE PAGE ...

Mast cell tumors (MCTs) are among the most commonly treated malignancies in practice.^{1,2} Histopathologic Patnaik grading is the most reliable prognostic indicator.³ In this system, Grade I tumors are indolent with low metastatic potential, whereas Grade III tumors are highly metastatic and locally aggressive.^{4,5} Grade II tumors, which represent the majority, have presented a challenge because of their variable behavior and a large interobserver disparity among pathologists.^{6,7} Subsequently, a 2-tier grading system and proliferation indices (Ki67 and mitotic index) are being incorporated individually or as part of a prognostic panel to facilitate prognostication and treatment planning.^{7,8}

Few studies have evaluated prognostic factors in dogs with stage IV disease (distant metastasis) or at high risk for metastasis, and there is no randomized study evaluating systemic treatments in these groups. This study sought to better define these groups for prognostic factors, outcome with common systemic treatments, and survival advantage in dogs treated with surgery and systemic therapy vs systemic therapy alone.

Dogs undergoing systemic therapy without gross disease had significantly better survival time as compared with those with gross disease (MST, 462 vs 150 days). Of note, dogs with metastatic disease that underwent surgical removal of only the primary tumor along with systemic therapy had a significant survival advantage vs those that did not undergo surgery (MST, 278 vs 91 days), regardless of completeness of margins and clinical stage. Dogs with Grade II nonmetastatic disease showed a survival advantage when receiving vinblastine and prednisone as compared with those receiving masitinib (MST, 1946 vs 369 days).

A more recent study supported these findings.⁹ Multivariate analysis of dogs with Stage IV disease found a measurable primary tumor at time of diagnosis to be negatively associated with progression-free interval (median, 21 vs 125 days) and overall survival (MST, 93 vs 180 days); dogs receiving local (surgery and/or radiation therapy) and systemic treatment had better outcomes.⁹ These results suggest that surgical resection of the primary MCT followed by systemic therapy offers a significant survival advantage, regardless of metastasis, as compared with dogs receiving only systemic therapy.

... TO YOUR PATIENTS

Key pearls to put into practice:

- 1 Histologic reports, especially of Grade II MCTs, must be critically evaluated.
- 2 If clinical presentation is not in agreement with the assigned grade, histologic proliferation indices (eg, Ki67 and mitotic index, MCT prognostic panel) should be requested.
- 3 In addition to systemic therapy, primary tumor control should be carefully considered even in dogs presenting with advanced Stage IV disease, as some will benefit if both are pursued.

References

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3. Patnaik AD, Ehler WJ, MacEwen EG. Canine cutaneous mast cell tumor: morphologic grading and survival time in 83 dogs. *Vet Pathol.* 1984;21(5):469-474.
4. Bostock DE. The prognosis following surgical removal of mastocytomas in dogs. *J Small Anim Pract.* 1973;14(1):27-41.
5. Bostock DE. Neoplasms in the skin and subcutaneous tissues in dogs and cats. *Br Vet J.* 1986;142(1):1-19.
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9. Pizzoni S, Sabattini S, Stefanello D, et al. Features and prognostic impact of distant metastases in 45 dogs with de novo stage IV cutaneous mast cell tumours: a prospective study. *Vet Comp Oncol.* 2017. doi:10.1111/vco.12306

Brief Summary of Prescribing Information

convenia[®]

(cefovecin sodium)

Antimicrobial for Subcutaneous Injection in Dogs and Cats Only

CAUTION: Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

INDICATIONS:

Dogs

CONVENIA is indicated for the treatment of skin infections (secondary superficial pyoderma, abscesses, and wounds) in dogs caused by susceptible strains of *Staphylococcus intermedius* and *Streptococcus canis* (Group G).

Cats

CONVENIA is indicated for the treatment of skin infections (wounds and abscesses) in cats caused by susceptible strains of *Pasteurella multocida*.

CONTRAINDICATIONS: CONVENIA is contraindicated in dogs and cats with known allergy to cefovecin or to β -lactam (penicillins and cephalosporins) group antimicrobials. Anaphylaxis has been reported with the use of this product in foreign market experience. If an allergic reaction or anaphylaxis occurs, CONVENIA should not be administered again and appropriate therapy should be instituted. Anaphylaxis may require treatment with epinephrine and other emergency measures, including oxygen, intravenous fluids, intravenous antihistamine, corticosteroids, and airway management, as clinically indicated. Adverse reactions may require prolonged treatment due to the prolonged systemic drug clearance (65 days).

WARNINGS: Not for use in humans. Keep this and all drugs out of reach of children. Consult a physician in case of accidental human exposure. For subcutaneous use in dogs and cats only. Antimicrobial drugs, including penicillins and cephalosporins, can cause allergic reactions in sensitized individuals. To minimize the possibility of allergic reactions, those handling such antimicrobials, including cefovecin, are advised to avoid direct contact of the product with the skin and mucous membranes.

PRECAUTIONS: Prescribing antibacterial drugs in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to treated animals and may increase the risk of the development of drug-resistant animal pathogens.

The safe use of CONVENIA in dogs or cats less than 4 months of age and in breeding or lactating animals has not been determined. Safety has not been established for IM or IV administration. The long-term effects on injection sites have not been determined. CONVENIA is slowly eliminated from the body, approximately 65 days is needed to eliminate 97% of the administered dose from the body. Animals experiencing an adverse reaction may need to be monitored for this duration.

CONVENIA has been shown in an experimental *in vitro* system to result in an increase in free concentrations of carprofen, furosemide, doxycycline,

and ketoconazole. Concurrent use of these or other drugs that have a high degree of protein-binding (e.g. NSAIDs, propofol, cardiac, anticonvulsant, and behavioral medications) may compete with cefovecin-binding and cause adverse reactions.

Positive direct Coombs' test results and false positive reactions for glucose in the urine have been reported during treatment with some cephalosporin antimicrobials. Cephalosporin antimicrobials may also cause falsely elevated urine protein determinations. Some antimicrobials, including cephalosporins, can cause lowered albumin values due to interference with certain testing methods.

Occasionally, cephalosporins and NSAIDs have been associated with myelotoxicity, thereby creating a toxic neutropenia^a. Other hematological reactions seen with cephalosporins include neutropenia, anemia, hypoproteinaemia, thrombocytopenia, prolonged prothrombin time (PT) and partial thromboplastin time (PTT), platelet dysfunction and transient increases in serum aminotransferases.

ADVERSE REACTIONS:

Dogs

A total of 320 dogs, ranging in age from 8 weeks to 19 years, were included in a field study safety analysis. Adverse reactions reported in dogs treated with CONVENIA and the active control are summarized in Table 2.

Table 2: Number of Dogs* with Adverse Reactions Reported During the Field Study with CONVENIA.

Adverse Reaction	CONVENIA (n=157)	Active Control (n=163)
Lethargy	2	7
Anorexia/Decreased Appetite	5	8
Vomiting	6	12
Diarrhea	6	7
Blood in Feces	1	2
Dehydration	0	1
Flatulence	1	0
Increased Borborygmi	1	0

*Some dogs may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Mild to moderate elevations in serum γ -glutamyl trans-ferase or serum alanine aminotransferase were noted post-treatment in several of the CONVENIA-treated dogs. No clinical abnormalities were noted with these findings.

One CONVENIA-treated dog in a separate field study experienced diarrhea post-treatment lasting 4 weeks. The diarrhea resolved.

Cats

A total of 291 cats, ranging in age from 2.4 months (1 cat) to 21 years, were included in the field study safety analysis. Adverse reactions reported in cats treated with CONVENIA and the active control are summarized in Table 3.

Table 3: Number of Cats* with Adverse Reactions Reported During the Field Study with CONVENIA.

Adverse Reaction	CONVENIA (n=157)	Active Control (n=163)
Vomiting	10	14
Diarrhea	7	26
Anorexia/Decreased Appetite	6	6
Lethargy	6	6
Hyper/Acting Strange	1	1
Inappropriate Urination	1	0

*Some cats may have experienced more than one adverse reaction or more than one occurrence of the same adverse reaction during the study.

Four CONVENIA cases had mildly elevated post-study ALT (1 case was elevated pre-study). No clinical abnormalities were noted with these findings.

Twenty-four CONVENIA cases had normal pre-study BUN values and elevated post-study BUN values (37–39 mg/dL post-study). There were 6 CONVENIA cases with normal pre- and mildly to moderately elevated post-study creatinine values. Two of these cases also had an elevated post-study BUN. No clinical abnormalities were noted with these findings.

One CONVENIA-treated cat in a separate field study experienced diarrhea post-treatment lasting 42 days. The diarrhea resolved.

FOREIGN MARKET EXPERIENCE: The following adverse events were reported voluntarily during post-approval use of the product in dogs and cats in foreign markets: death, tremors/ataxia, seizures, anaphylaxis, acute pulmonary edema, facial edema, injection site reactions (alopecia, scabs, necrosis, and erythema), hemolytic anemia, salivation, pruritus, lethargy, vomiting, diarrhea, and inappetence.

For a copy of the Material Safety Data Sheet, (MSDS) or to report a suspected adverse reaction call Zoetis Inc. at 1-888-963-8471.

STORAGE INFORMATION:

Store the powder and the reconstituted product in the original carton, refrigerated at 2° to 8° C (36° to 46° F). Use the entire contents of the vial within 56 days of reconstitution. PROTECT FROM LIGHT. After each use it is important to return the unused portion back to the refrigerator in the original carton. As with other cephalosporins, the color of the solution may vary from clear to amber at reconstitution and may darken over time. If stored as recommended, solution color does not adversely affect potency.

HOW SUPPLIED:

CONVENIA is available as a 10 mL multi-use vial containing 800 milligrams of cefovecin as a lyophilized cake.

NADA# 141-285, Approved by FDA

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Kalamazoo, MI 49007

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