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Prophylactic Trimethoprim-Sulfadiazine during Chemotherapy in Dogs with Lymphoma and Osteosarcoma: A Double-Blind, Placebo-Controlled Study

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Background: The administration of chemotherapy is associated with risk for morbidity. Management of chemotherapy-related morbidity in veterinary oncology has been primarily supportive.

Hypothesis: The purpose of this study was to evaluate the effect of prophylactic antimicrobial use on chemotherapy-associated morbidity in dogs with lymphoma or osteosarcoma.

Animals: Dogs presenting with histologically confirmed osteosarcoma or lymphoma were eligible.

Methods: Patients were randomized to receive placebo or trimethoprim-sulfadiazine for 14 days after their first doxorubicin chemotherapy. Both owner and clinician were blinded with respect to treatment. Patient assessment included CBC, physical examination and performance, and toxicosis grading on days 7 and 14. Investigated outcomes were hospitalization, suspicion of infection, gastrointestinal toxicity, neutropenia, nonhematologic toxicity, and quality of life.

Results: Seventy-three dogs were enrolled; 34 had osteosarcoma, and 39 had lymphoma. Dogs receiving trimethoprim-sulfadiazine (n = 36) had a significantly reduced hospitalization rate ($P = .03$), nonhematologic toxicity ($P = 0.039$), grade 2–4 nonhematologic toxicity ($P < .0001$), grade 2–4 gastrointestinal toxicity ($P = .007$). and altered performance ($P = .015$). By group, dogs with osteosarcoma (n = 34) that received the antimicrobial experienced fewer occurrences of nonhematologic toxicity ($P = .02$) and less severe nonhematologic toxicity ($P = .038$). Dogs with lymphoma (n = 39) had significant reductions in the occurrence of hospitalization ($P = .035$), severity of nonhematologic toxicity ($P = .036$), and alterations of performance ($P = .015$).

Conclusions: The use of prophylactic trimethoprim-sulfadiazine has benefit in reducing morbidity in dogs with osteosarcoma or lymphoma during the first 14 days after treatment with doxorubicin.

Key words: Antimicrobials; Doxorubicin; Gastrointestinal toxicity; Hospitalization; L-asparaginase; Myelosuppression.

Lymphoma and osteosarcoma are common malignancies in the dog.[1–3] Tumor response and improved patient survival have been demonstrated when chemotherapy is administered as sole therapy for multicentric lymphoma or as an adjunct to surgery for appendicular osteosarcoma.[4,5]

The administration of chemotherapeutics is costly and associated with risk for morbidity that may alter patient quality of life, lead to treatment delays or discontinuation, and possibly result in death. Thus far, the management of chemotherapy-related morbidity in veterinary cancer patients has been primarily supportive. Much attention has been devoted in human oncology to mitigating these effects of cytotoxic treatment. Specifically, numerous attempts have been made with the administration of prophylactic antimicrobials. Potentiated sulfonamides and more recently fluoroquinolones are commonly studied. These studies have demonstrated significant reductions in mortality, hospitalization, infection, and cost of patient care.[6–10] Owing to concerns about the emergence of resistant infections with routine prophylactic antimicrobial use, recommendations have been made to limit antimicrobials to patients who are young, immunologically compromised, or expected to develop clinically relevant and prolonged myelosuppression. In spite of these recommendations, a recent study indicated that 45% of physicians dispense prophylactic antimicrobial care to human chemotherapy patients.[11]

A controlled study evaluating the effect of prophylactic antimicrobial use in veterinary oncology or the selective pressure it may add to the emergence of resistant infections has not been performed. However, potentiated sulfonamide combinations, in particular trimethoprim-sulfadiazine (TMS), often are recommended. We conducted a randomized, double-blind, placebo-controlled trial to evaluate the effect on treatment-related morbidity of prophylactic trimethoprim-sulfadiazine administered during the first 14 days after doxorubicin chemotherapy in dogs with lymphoma or osteosarcoma.

Materials and Methods

This study included dogs with histologically confirmed lymphoma or appendicular osteosarcoma presented to the Harrington

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Table 1. Modified Karnofsky's performance criteria.[49]

Grade	Criteria
0	Fully active, performs at predisease level
1	Activity less than predisease level; able to function as acceptable pet
2	Severely compromised activity; ambulatory only to point of eating, sleeping, and consistently eliminating in acceptable areas.
3	Completely disabled; must be force fed; unable to control eliminations to acceptable areas.
4	Dead

Oncology Program, Tufts University (TUSVM), University of Tennessee, or the Comparative Oncology Unit, Colorado State University, between December 1997 and February 1999. All dogs with osteosarcoma were staged by a CBC, serum biochemistry, urinalysis, 3-view thoracic radiographs, and amputation of their affected limb. All dogs with lymphoma were staged by a CBC, serum biochemistry, urinalysis, 2-view abdominal and thoracic radiographs, bone marrow aspiration, and surgical lymph node excision. Staging was determined by the modified World Health Organization system for canine lymphoma and by published criteria for surgical staging of osteosarcoma.[12,13] All owners were required to provide informed consent for enrollment. The study was approved by the Institutional and Animal Care and Use Committee at TUSVM.

The study encompassed the first 14 days after the initiation of chemotherapy. Dogs with lymphoma began chemotherapy immediately after staging. Dogs with osteosarcoma received their first chemotherapy treatment 10–14 days after amputation of their affected limb. All patients received doxorubicin at a dosage of 30 mg/m^2 body surface area IV on day 0. Those diagnosed with lymphoma also received L-asparaginase (10,000 IU/m^2 body surface area SC or IM) on day 0 and again on day 7. When doxorubicin and L-asparaginase where administered on the same day (day 0), doxorubicin was administered a minimum of 6 hours before L-asparaginase by study design because of perceived concern that L-asparaginase may enhance doxorubicin toxicity when given concurrently.

All dogs were randomized to receive either ascorbic acid[a] (placebo group) or TMS[b] (treatment group) using a pairwise randomization scheme. To ensure equal allotment, a separate randomization scheme was used for animals weighing <12 kg. Vials containing TMS or placebo were prepackaged in numbered vials by a single pharmacy (TUSVM). The study was double-blinded. Both TMS and ascorbic acid were administered at 20–30 mg/kg PO q12h for the 14-day study period or until suspicion of infection occurred. The blinding was broken when the patient was suspected to have acquired infection. Decisions were based on individual clinician assessment and changes in physical, clinical, and hematologic findings such as fever (≥103°F) with or without neutropenia. At the time of unblinding, the study drug or placebo was discontinued and replaced with broad-spectrum antibiotics at the discretion of the attending clinician. Decisions to hospitalize were based on the severity of clinical changes and individual clinician assessment.

All animals had complete physical examinations and CBC performed 7 and 14 days after beginning chemotherapy. All owners were required to answer questionnaires regarding compliance with the study criteria and their pet's performance between visits. On days 7 and 14 after treatment, patients were assigned a modified Karnofsky's Performance grade (Table 1) and toxicosis grade (Table 2) based on these findings. Outcomes evaluated were occurrence and grade of hospitalization, suspected infection, gastrointestinal toxicity (e.g. anorexia, vomiting, diarrhea), neutropenia (neutrophil count ≤2,500/μL), any nonhematologic toxicity (eg, gastrointestinal toxicity, hospitalization, suspected infection) and quality of life as assessed by the modified Karnofsky's Performance criteria.

Table 2. Modified Eastern Cooperative Oncology Group evaluation.[50]

Toxicity/Grade	Signs/Duration
Hospitalization	Days
0	0
1	1
2	2–3
3	4–5
4	>5
Neutropenia	
0	>2,500 neutrophils/μL
1	1,500–2,500 neutrophils/μL
2	1,000–1,499 neutrophils/μL
3	500–999 neutrophils/μL
4	<500 neutrophils/μL
Anorexia	
0	None
1	Inappetance
2	Anorexia <3 days duration
3	Anorexia >3 days but <5 days duration
4	Anorexia >5 days duration; 10% weight loss
Vomiting	
0	None
1	Nausea
2	Sporadic, self-limiting
3	1–5 episodes per day, <2 days
4	6–10 episodes per day, hospitalized
Diarrhea	
0	None
1	Soft stools, responds to dietary modification
2	1–4 watery stools per day, <2 days
3	4–7 watery stools per day or >2 days
4	>7 watery stools per day or bloody, hospitalized
Infection	
0	None
1	No medication
2	Required medication
3	Debilitating
4	Threatening

All outcomes were evaluated as categorical data. Statistical calculations were applied to the entire study population and populations stratified by neoplasia type.[c] Pearson's χ^2 analysis was used, when possible, for all statistical calculations. For small sample sizes, Fisher's exact test was used. A P value of ≤ .05 was considered significant. Both the presence and absence of outcomes and their severity were assessed for significance. To enable evaluation as a categorical variable, severity of outcome was categorized as grades 0 or 1 versus 2, 3, or 4 (Table 2). Variables investigated were lymphoma stage (III versus IV versus V), lymphoma substage (a versus b), type of cancer (lymphoma versus osteosarcoma), antibiotic versus placebo, sex (male versus female), neutropenia (≤2,500 cells/μL), and body weight (≤12 kg versus >12 kg). Weight also was evaluated as a continuous variable using the 2-sample t-test. When more than one variable was determined to significantly affect outcome, multivariate analysis using logistic regression was performed.

Table 3. Patient distribution.

Parameter	TMS (n = 36)	Placebo (n = 37)
Osteosarcoma	18	16
Lymphoma	18	21
Gender		
Male	14	14
Female	22	23
Age (years)		
Median	8	9
Range	4-15	3-11
Weight (kg)		
≤12	3	1
Median	36.1	31
Range	10–52.4	9.5–46.9

TMS, trimethoprim-sulfadiazine.

Results

Patient Population

Seventy-three dogs were enrolled. Thirty-four dogs had osteosarcoma, and 39 had lymphoma. Thirty-six received prophylactic TMS, and 37 received placebo. Twenty-three different breeds were represented. There were no significant differences in patient demographics between the groups receiving TMS and placebo (Table 3). All dogs with osteosarcoma were staged as IIb. Twelve breeds were represented in this group. The most common were mixed breeds (24%), Golden Retrievers (24%), Rottweilers (18%), and Labrador Retrievers (9%). Females were overrepresented (70%). Median age was 8.5 years (range, 3–13 years). Median weight was 34.9 kg (range, 17.9–55.6 kg). Staging results for those diagnosed with lymphoma are summarized in Table 4. Thirty-seven were substage a, and 2 were substage b. Seventeen breeds were present in this group. Most common were mixed breeds (26%), Golden Retrievers (13%), and Rottweilers (8%). Females were slightly overrepresented (53%).

Table 4. Lymphoma patient distribution.

Parameter	TMS (n = 18)	Placebo (n = 21)
Sex		
Male	8	10
Female	10	11
Age (years)		
Median	8	9
Range	4–15	3–11
Weight (kg)		
Median	30.3	30.8
Range	10–52.4	9.5–46.9
Stage		
I	0	1
II	0	0
III	9	9
IV	5	7
V	4	4
Substage a	16	21
Substage b	2	0

TMS, trimethoprim-sulfadiazine.

Nonhematologic Toxicity

Overall, 41 dogs (56%) experienced 100 episodes of nonhematologic toxicity (eg, gastrointestinal toxicity, hospitalization, suspected infection) during the study. The only variable found to significantly affect this outcome was TMS. Dogs receiving TMS experienced less nonhematologic toxicity when compared to those receiving placebo (n = 16, 44% versus n = 25, 68%, respectively; $P = .039$). When evaluating for severity, grade 2–4 nonhematologic toxicity was less likely to occur in those animals receiving TMS (n = 6, 16% versus n = 21, 56%; $P < .0001$). When stratified by tumor type, dogs with osteosarcoma receiving placebo had a higher occurrence (n = 11, 69% versus n = 5, 28%) and more severe nonhematologic toxicity (n = 7, 43% versus n = 2, 11%) when compared to those that received TMS ($P = .02$ and $P = .038$, respectively).

In the lymphoma group, stage IV was associated with a higher occurrence of nonhematologic toxicity (12 of 18 stage III [67%], 11 of 12 stage IV [92%], 2 of 8 [25%] stage V; $P = .009$). With severity, both stage IV and TMS administration were found to be significant. However after multivariate analysis, only TMS administration resulted in fewer occurrences of grade 2–4 nonhematologic toxicity (6 of 18, 33% receiving TMS versus 14 of 21, 66% receiving placebo; $P = .036$).

Gastrointestinal Toxicity

Overall, 43 dogs experienced 88 episodes of gastrointestinal toxicity (Table 5). Thirty-nine episodes (44%) in 28 dogs were grade 1; 24 episodes (27%) in 19 dogs were grade 2; 7 episodes (8%) in 5 dogs were grade 3; and 18 episodes (20%) in 12 dogs were grade 4. Eleven dogs (92%) with grade 4 toxicity, 4 (80%) with grade 3, 13 (68%) with grade 2, and 10 (36%) with grade 1 toxicity were receiving placebo. No variables were found to be associated with gastrointestinal toxicity. With severity, grade 2–4 gastrointestinal toxicity occurred less often in those receiving TMS versus placebo (n = 6, 17% versus n = 17, 46% respectively; $P = .007$).

Within the osteosarcoma group, no variable affected occurrence or severity of gastrointestinal toxicity. Stage IV was the only variable that affected this outcome in the lymphoma group. Specifically, 12 of 18 stage III dogs (67%), 11 of 12 stage IV dogs (92%), and 2 of 8 stage V dogs (25%) experienced toxicity ($P = .009$).

Hospitalization

Eight animals (11%) were hospitalized for 9 hospitalization episodes (median, 2 days; range, 1–6 days; Table 5). All patients hospitalized had grade 3 gastrointestinal toxicity. One animal was receiving TMS, and 7 were receiving placebo ($P = .03$). Animals receiving

Table 5. Gastrointestinal toxicity and hospitalization.

	Grade 1 (N/N)		Grade 2 (N/N)		Grade 3 (N/N)		Grade 4 (N/N)			
Parameters	P	TMS	P	TMS	P	TMS	P	TMS	P	TMS
Anorexia	2/2	4/4	8/8	3/3	3/3	0/0	4/3	0/0		
Vomiting	7/7	13/9	5/5	1/1	1/1	1/1	2/2	0/0		
Diarrhea	5/5	8/8	4/4	3/3	1/1	1/1	11/9	1/1		
Total	14/11	25/17	17/13	7/6	5/4	2/1	17/11	1/1		
Hospitalized Dogs										
Dog 1				A		D V				[a]
Dog 2			A				D V		[a]	
Dog 3					A I				[a]	
Dog 4			A				D V		[a]	
Dog 5			V		D				[a]	
Dog 6			D V				D		[a]	
Dog 7			V		A		D		[a]	
Dog 8					A V I				[a]	

N/N, Number of episodes/number of patients; P, placebo; TMS, trimethoprim-sulfadiazine; A, anorexia; D, diarrhea; V, vomiting; I, suspected infection.

[a] Placebo or antibiotic in column.

placebo had a median hospitalization duration of 2 days (range, 1–6 days). One patient in this group was hospitalized twice for grade 4 gastrointestinal toxicity during the first 7 days and grade 2 during days 8–14. The patient hospitalized while receiving TMS was hospitalized 2 days because of grade 3 gastrointestinal toxicity. No hospitalized patient receiving TMS developed neutropenia and fever, whereas 2 (5%) receiving placebo were hospitalized with this finding. The duration of hospitalization was not significantly different between groups.

Stratified by tumor type, no variable was identified in dogs with osteosarcoma. Within the lymphoma group, TMS versus placebo was significant. In this group, 5 patients (13%) were hospitalized for a median of 2 days (range, 1–3 days). All 5 received placebo ($P = .035$).

Karnofsky's Performance

Karnofsky's performance grade was not established at enrollment in this study. During the 14-day follow-up, 21 dogs experienced 25 episodes of altered Karnofsky's performance grade. Twenty-one episodes (84%; 17 dogs) were grade 1. Four episodes (16%; 4 dogs) were grade 2. Six dogs (14%) received TMS, and 15 dogs (40%) received placebo ($P = .015$).

Within the stratified groups, no significant variable was identified in dogs with osteosarcoma. TMS versus placebo was found to be significant within the lymphoma group. Eleven dogs (28%) in this group had altered performance (9 receiving placebo versus 2 receiving TMS, $P = .015$).

Suspected Infection

Seven dogs (10%) developed suspected infection during the study. It was limited to the surgical site (ie, lymph node excision or amputation) in 3 dogs, respiratory tract in 3 dogs, and intestinal tract in 1 dog. Two dogs received TMS, and 5 received placebo. Two dogs required hospitalization. Both had suspected respiratory infections and grade 3 intestinal toxicity and were receiving placebo. These differences were not significant in the overall population or in stratified groups. Seven episodes of fever occurred. All had received placebo. One of these 7 patients had suspected infection (ie, lymph node excision site).

Neutropenia

Overall, the median neutrophil count before therapy was 7,200/μL (range, 3,200–22,200/μL). On days 7 and 14 the median neutrophil counts were 2,400/μL (range, 100–13,200/μL) and 7,420/μL (range, 890–19,800/uL), respectively. Forty-two episodes of neutropenia were seen in 39 animals. Twenty-seven episodes (64%; 25 dogs) were grade 1. Eight episodes (19%; 8 dogs) were grade 2, 3 (7%; 3 dogs) were grade 3, and 4 episodes (9%; 4 dogs) were grade 4. Fifty percent of animals receiving TMS and 57% of animals receiving placebo developed neutropenia ($P = .31$).

By group, the median neutrophil counts on days 0, 7, and 14 were 6,980/μL (range, 2,520–18,230/μL), 2,430/μL (range, 220–13,200/μL), and 6,840/μL (range, 3,150–14,000/μL), and 7,800/μL (range, 3,740–18,920/μL), 2,340/μL (range, 100–12,500/μL), and 8,400/μL (range, 890–19,800/μL) for osteosarcoma and lymphoma groups, respectively. None of the investigated variables was found to significantly affect this outcome overall or in groups. Fever occurred in 3 animals, 1 each with grade 1, 2, and 4 neutropenia. All 3 animals received placebo. No episode of neutropenia and fever occurred in animals receiving TMS.

Discussion

Prophylactic TMS administered during the first 14 days of chemotherapy significantly reduced the occurrence and severity of nonhematologic toxicity,

the severity of gastrointestinal toxicity, and the hospitalization rate. Additionally, dogs receiving TMS had higher performance grades during therapy than did placebo groups. Dogs with osteosarcoma receiving TMS experienced significantly fewer occurrences and less severe nonhematologic toxicity. Dogs with lymphoma revealed significant reductions in severity of nonhematologic toxicity, hospitalization, and performance alterations if receiving TMS. This finding indicates that the use of prophylactic TMS has benefit in reducing morbidity during doxorubicin induction in dogs with osteosarcoma but has the greatest benefit during doxorubicin/L-asparaginase induction in dogs with lymphoma.

This outcome is in agreement with studies in humans that have demonstrated that patients most likely to benefit from prophylactic antimicrobial therapy are those undergoing induction therapy for hematopoietic malignancies.[6,14–19] Those patients are at a higher risk of sepsis and death because of more intensive chemotherapy regimens and more extensive systemic involvement, which lead to more serious and longer alterations in normal protective mechanisms such as surface barriers (ie, keratin and mucosal surfaces), leukocytes, and humoral factors as compared to patients with solid malignancies. These changes, particularly in the intestinal tract, lead to micro-ulcerations and loss of the normal ''feeder layer'' (ie, desquamated cells, saliva, and mucus), which collectively create a favorable environment for aerobic gram-negative bacilli and gram-positive cocci overgrowth and translocation.[20–22] By specifically using TMS combinations, which inhibit intestinal bacterial adherence, are broad spectrum, and spare normal anaerobic gastrointestinal flora, aerobic bacterial overgrowth and invasion are suppressed.[23]

As observed in humans, a higher risk for morbidity has been demonstrated in the treatment of canine hematopoietic malignancies.[24–27] These animals (as opposed to those with solid tumors) may have additional predispositions to morbidity because of their larger tumor burdens, which render them at a higher risk for paraneoplastic alterations in metabolism and immune functions.[20,28,29] These described changes in patients with hematopoietic malignancies may explain the more substantial benefit identified in this study for animals with lymphoma as opposed to those with osteosarcoma. Specifically, our study documented 47% of dogs with osteosarcoma versus 67% with lymphoma developed gastrointestinal toxicity, 47% versus 69% developed nonhematologic toxicity, and 3 versus 5 were hospitalized, respectively. However, these findings were not found to be statistically significant.

This study found that higher stage (eg, stage IV lymphoma) was significantly associated with a higher occurrence of nonhematologic and gastrointestinal toxicity regardless of TMS or placebo treatment. This finding is in agreement with previous veterinary studies on similar populations of dogs and may be attributed to paraneoplastic alterations, compromised barriers, and a more debilitated state of the patient at the onset of chemotherapy.[24,27,30] This association was not demonstrated here with stage V dogs, possibly because of the lower numbers of stage V patients.

A limitation of the present study was the failure to specifically assess the occurrence of sepsis. Overall, the prevalence of sepsis and the resulting mortality in animals as compared to human patients undergoing chemotherapy is much lower (sepsis 1–9% versus 45% and mortality 2–4% versus 30%).[26,28,31–36] No death occurred during this study. Therefore, it is difficult to explain why animals in both groups and overall demonstrated benefit if receiving prophylaxis. We speculate that perhaps the benefit incurred here resulted from prophylactic treatment of endotoxemia. This speculation is based in part on the assumption that similar biologic changes that lead to sepsis also may place patients at high risk for endotoxemia (ie, enteric gram-negative bacterial overgrowth and altered mucosal integrity enabling endotoxin absorption or enteric bacteria translocation). Although no studies were identified evaluating the incidence of endotoxemia in veterinary cancer patients, studies in humans indicate that endotoxemia commonly occurs in patients with hematopoietic malignancies and in patients who receive chemotherapy.[37,38] The occurrence of sepsis in dogs receiving TMS was reduced in one single study evaluating 3 doxorubicin-containing chemotherapeutic protocols.[39]

Suspected infection was an investigated outcome. Although not significant, 7 episodes occurred. Five (71%) occurred in animals receiving placebo as opposed to 2 (29%) in animals that received TMS.

The cost benefit of outpatient care versus hospitalization is an end point evaluated in human studies. Both have been demonstrated to be significantly reduced with oral prophylactic antimicrobial therapy.[6–10,17,40] The hospitalization rate in this study was found to be significantly reduced, specifically in dogs with lymphoma. Nine episodes of hospitalization occurred. Eight episodes (89%) occurred while receiving placebo, whereas only one (11%) occurred while receiving TMS. This dog (with osteosarcoma) was hospitalized for severe (grade 4) gastrointestinal toxicity.

All animals hospitalized demonstrated severe gastrointestinal toxicity (grade 3 or 4). Therefore, it appears that the hospitalized animals had grade 3 gastrointestinal toxicity in common. Clinicians may have been more likely to hospitalize patients if they were known to be on the placebo (1 animal hospitalized and receiving placebo was not switched to antibiotics). However, clinicians also may have been less likely to hospitalize these patients but rather send them home on antibiotics if antibiotics were not already being administered. Eight additional patients in this study experienced grade 3 or higher gastrointestinal toxicity and were not hospitalized. Seven were receiving placebo. Two of these 8 animals were switched to antibiotics. One was receiving TMS and the other placebo. Although not an end point of this study, the cost of PO administered TMS versus the cost of hospitalization favors the prophylactic administration of TMS.

A lack of sensitivity and second-person assessment are limitations in any attempt to evaluate quality of life in an animal. Nonetheless, it is an important variable to

investigate. We elected to use a modified Karnofsky's grading system, which has been used previously in dogs.[28] Animals with lymphoma that were receiving TMS had significantly better performance scores during therapy as compared to those receiving placebo. This finding lends further support that the modified Karnofsky's system may be a valuable tool to assess quality of life in future studies.

Ascorbic acid was selected as a placebo based on safety, low cost, and similarity in color, size, and consistency to TMS. The safety of ascorbic acid is supported by Demole and others who used dosages of up to 5 gm/kg in animals, including cats and dogs, without causing toxicity[41,42] and by recommendations of dosages of 25–60 mg/kg (up to 10 g daily) for canine inflammatory bowel disease, hepatobillary disease, and hip dysplasia.[43,44] Ascorbic acid does appear to play a role in a number of neutrophil functions, including increased chemotaxis, increased particulate ingestion, and enhanced lysozyme-mediated nonoxidative killing. However, these benefits often are associated with much higher dosages and longer administration durations than those used in this study and therefore may explain the lack of benefit identified in those receiving placebo compared to TMS.

Potentiated sulfonamide combinations, in particular TMS, often are recommended in veterinary oncology. Their common use in conjunction with severely myelosuppressive chemotherapeutic agents and in phase I veterinary trials is because of their bactericidal, broad spectrum antimicrobial coverage; high oral bioavailability; ability to preserve colonization resistance; and ability to reduce intestinal bacterial adherence.[6–8,45,46] No toxicity was attributed to TMS in this study. However, dose-dependent and idiosyncratic reactions have been reported.[47] These reactions may be manifested as early as 5 days (mean, 12.1 days; range, 5–36 days). Owing to the relative rarity and short courses of therapy used in veterinary oncology, routine diagnostic monitoring in patients without clinical changes does not appear to be warranted.[47]

Concerns may arise from the potential to induce resistant infections in patients or increase selection pressure for resistance by administering short-term courses of prophylactic antimicrobials. Attempts have been made to address these concerns concurrently with investigations on oral prophylaxis in studies of human patients.[7,40,45] Using microbiologic assays on isolates from bacteremic patients as well as on periodic stool cultures, the findings have not demonstrated significant overgrowth of TMS-resistant organisms or increased risk of infections by such organisms. A reduction in the incidence of hospitalization and the use of a broad-spectrum antimicrobial in that setting may in fact reduce selection pressure for bacterial resistance.[11]

Significant increases in TMS-resistant organisms have not been demonstrated in these studies of human patients. In animals, routine antibiotic use, particularly enrofloxacin, may be contributing to the increasing prevalence of multidrug-resistant *Escherichia coli* infections in veterinary hospitals.[48] This finding has not been investigated with the potentiated sulfonamides. Nonetheless, discretion and careful case selection should be used when dispensing any antimicrobial agent until more studies evaluating their impact are performed.

This study was designed to investigate the effects of the administration of prophylactic TMS to veterinary cancer patients. For the sake of intensive chemotherapy, grade 2 toxicities often are acceptable to the clinician and may not necessarily represent an unacceptable adverse event. Therefore, the most clinically relevant finding of this study may be the reduction of the hospitalization rate. However, given that the primary goal of chemotherapy in veterinary oncology is remission with palliation, all toxicities were grouped as grades 0 or 1 versus grades 2, 3, or 4. Although grade 2 toxicities are not life threatening and often self limiting, they are deemed to be clinically relevant as they compromise patient quality of life and owner willingness to continue intensive chemotherapy regimens. Examples include the difference between inappetence (grade 1) versus complete anorexia (grade 2), soft stools (grade 1) versus watery diarrhea (grade 2), and nausea (grade 1) versus overt vomiting (grade 2).

This study suggests that the use of oral prophylactic TMS is beneficial for reducing multiple toxicities during induction chemotherapy with doxorubicin with or without L-asparaginase in the dog and could be considered in other clinical settings. Additional studies are necessary to evaluate its benefit with more myelosuppressive drugs and in more debilitated patients. Based on studies in humans using short courses of therapy, we do not believe the administration of TMS increases the risk of resistant bacteria in oncology patients. Given the lack of microbiologic studies in dogs addressing potential resistance, however, dogs receiving prophylactic antimicrobial care should be monitored carefully.

Footnotes

[a] CVS Pharmacy, Woonsocket, RI
[b] Tribrissen; Schering-Plough, Kenilworth, NJ
[c] SPSS 10, Statistical Analytical Software, Chicago, IL

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