Case-control study to evaluate risk factors for the development of sepsis (neutropenia and fever) in dogs receiving chemotherapy

Karin U. Sorenmo, DVM, DACVIM; Lisa P. Harwood, VMD;
Lesley G. King, MVB, DACVECC, DACVIM; Kenneth J. Drobatz, DVM, MSCE, DACVIM, DACVECC

Objective—To identify risk factors for development of sepsis in dogs treated with chemotherapeutics and to evaluate the impact of sepsis on outcome.

Design—Case-control study.

Animals—Client-owned dogs with various cancers undergoing standard chemotherapeutic treatment at the University of Pennsylvania veterinary hospital.

Procedures—39 dogs with sepsis (cases) were identified through a search of the medical record database. Controls (n = 77) were randomly selected from dogs admitted during the same time period. Variables analyzed included patient demographics, tumor type, stage, remission status, treatment phase, chemotherapeutics used, and outcome.

Results—Dogs that weighed less and dogs with lymphoma were significantly more likely to become septic, compared with larger dogs or dogs with solid tumors. Septic dogs were also significantly more likely to have received doxorubicin (odds ratio [OR], 12.5; 95% confidence interval [CI], 2.4 to 66.0) or vincristine (OR, 9.0; 95% CI, 1.6 to 52.0) than controls. Of the 39 cases, 28 (71.8%) were in the induction phase of their protocol, and 19 of 39 (48.7%) became septic after receiving the chemotherapeutic drug for the first time. Median survival time of the cases (253 days) was not significantly different from that of the controls (371 days).

Conclusions and Clinical Relevance—Dogs that weighed less were at increased risk for chemotherapy-induced sepsis. Tumor type and chemotherapeutic drug used were also important risk factors. These results may lead to the implementation of prophylactic measures, especially when doxorubicin or vincristine is used in the induction phase in small dogs with lymphoma. (*J Am Vet Med Assoc* 2010;236;650–656)

Myelosuppression remains one of the major dose-limiting toxic effects of cytotoxic chemotherapy in veterinary and human oncology. Neutropenia and fever are common consequences of chemotherapy-induced myelosuppression, and these complications are associated with morbidity and fatalities in humans and other animals with cancer.[1,2] The incidence of sepsis resulting from myelosuppressive chemotherapy is relatively low in veterinary medicine, probably because of differences in the philosophy and goals for treatment of animals (ie, chemotherapeutic drugs are administered at lower dosages and in fewer combinations to maintain an acceptable quality of life and avoid repeated or prolonged hospitalization to treat chemotherapy-induced adverse effects).[1]

Nevertheless, the consequences of sepsis can be important for affected patients that require hospitalization for supportive care and IV administration of broad-spectrum antimicrobials. Chemotherapeutic treatment is typically discontinued until the animal has fully recovered from the toxicosis, at which time the doses may need to be reduced to avoid further episodes. Such treatment delays and dose reductions may adversely impact treatment efficacy and could theoretically result in relapse and a decrease in survival time. Furthermore, sepsis may be fatal, especially when the septic animal is not treated appropriately. Most animals recover after appropriate therapeutic measures, but some die despite treatment. Therefore, recognizing patients that might be at increased risk for development of sepsis would enable clinicians to institute appropriate preventive measures and thus avoid morbidity, hospitalization, increased costs, treatment delay, treatment discontinuation, and potentially decreased therapeutic efficacy as well as death in treated animals.

To our knowledge, a comprehensive study has not been conducted to determine animals that are at risk for development of sepsis and factors that may contribute to this risk. Therefore, the purpose of the study reported here was to evaluate selected potential risk fac-

Abbreviations

BSA	Body surface area
CI	Confidence interval
OR	Odds ratio
TMS	Trimethoprim-sulfadiazine

From the Department of Clinical Studies (Sorenmo, Harwood, King, Drobatz) and the Mari Lowe Center for Comparative Oncology (Sorenmo), School of Veterinary Medicine, Philadelphia, PA 19104. Dr. Harwood's present address is Paoli Vetcare, 1476 E Lancaster Ave, Paoli, PA 19301.

Address correspondence to Dr. Sorenmo (karins@vet.upenn.edu).

tors that could contribute to the development of sepsis and determine the impact of sepsis on survival time in dogs receiving chemotherapy.

Materials and Methods

Animals—Case dogs were retrospectively identified by searching the medical records of the Matthew J. Ryan Veterinary Hospital of the University of Pennsylvania from 1996 through 2003 for dogs hospitalized and treated because of chemotherapy-induced neutropenia and fever. Records were searched to identify dogs for which there was a charge indicated for a chemotherapeutic drug and that had a subsequent visit during which they were admitted, hospitalized overnight, and treated (as indicated by a charge for IV administration of fluids). Medical records were carefully reviewed to determine whether these case dogs were neutropenic and febrile during the subsequent visit during which they were treated. Neutropenia was defined as a neutrophil count < 2,500 cells/µL, and fever was defined as a rectal temperature of > 39.2°C (102.5°F). The combination of neutropenia and fever was assumed to be associated with sepsis; however, microbial culture of blood samples was not performed to confirm bacteremia or septicemia in most of these dogs. For dogs that had > 1 septic episode, only the first episode was included in the study.

Control dogs were randomly selected from the medical record database and consisted of dogs that received chemotherapeutic drugs at the same hospital during the same time period as the case dogs but without becoming septic. After the computer randomly identified a control dog, the information for the visit included in the study was randomly selected from all visits for that dog after chemotherapy was initiated; however, the visit was only included if it fulfilled the criteria that a CBC was performed and the visit immediately preceding this visit included a chemotherapeutic treatment. Medical records of all control dogs were reviewed to ensure that they had not been treated for sepsis secondary to chemotherapy during another visit or by their referring veterinarian. All case and control dogs were indentified by name and hospital number, which were cross-referenced to ensure that a case dog was not represented in the control population and vice versa. To optimize efficiency and statistical power, our original goal was to select 3 control dogs:1 case dog. This ratio between control and case animals has been found to provide cost-efficient results and adequate power in accordance with epidemiological statistical guidelines.[3]

Evaluation of risk factors—Risk factors for sepsis that were evaluated in the study included age, sex, breed, body weight, body condition, tumor type, tumor stage, remission status, treatment phase (for lymphomas and leukemias, induction, maintenance, and rescue; for solid tumors, adjuvant or primary [measurable tumor]), chemotherapeutic drug or protocol for use (eg, dosage), use of corticosteroids, and single chemotherapeutic agent versus a combination of chemotherapeutic agents. Outcome and survival time were evaluated for case and control dogs.

Statistical analysis—The unpaired Student *t* test was used to analyze differences between case and control dogs for normally distributed continuous data (ie, age), and results were reported as mean ± SD. The rank sum test was used to analyze differences between continuous variables that were not normally distributed (ie, body weight), and results were reported as median (range). The χ^2 test or Fisher exact test (if the expected value in a cell was < 5) was used to analyze differences between case and control dogs for categorical or binominal variables, including sex (sexually intact male, castrated male, sexually intact female, or spayed female), body condition (overweight, normal weight, underweight, or cachectic), breed, tumor type (lymphoma, leukemia, or solid tumor), treatment phase (induction, maintenance, or rescue), remission status (in remission or not in remission), chemotherapeutic drug used, use of corticosteroids, and a single chemotherapeutic agent versus a combination of chemotherapeutic agents. Multiple logistic regression was used to evaluate the risk for development of sepsis associated with the main chemotherapeutic drugs (doxorubicin, vincristine, cyclophosphamide, and other [other drugs included carboplatin, chlorambucil, vinblastine, lomustine, mechlorethamine, fluorouracil, L-asparaginase, cisplatin, actinomycin, and methotrexate]). Reported ORs for this analysis reflected the OR controlled for the other drugs and tumor type within the model. Multiple logistic regression was also performed to evaluate the effect of body weight and tumor type (lymphoma, leukemia, or solid tumor) on risk of development of sepsis.

Survival time was calculated from the date of surgery or initiation of chemotherapy to the date of death or last known status. Dogs still alive, lost to follow-up monitoring, or that died as a result of causes other than cancer or cancer treatment were censored at the last date on which they were known to be alive or the date on which they died as a result of another cause. The Kaplan-Meier product-limit method was used to estimate the portion of case and control dogs that were alive or had died. The log-rank test was used to analyze differences between the groups.

A statistical software program[a] was used for all calculations. Values of $P < 0.05$ were considered significant for all analyses.

Results

Animals—Forty case dogs were initially identified, but 1 dog with osteosarcoma of the appendicular skeleton that received an accidental overdose of carboplatin was excluded because it was believed that it might not be representative of the typical at-risk-for-sepsis population. There were 120 control dogs initially identified, but 43 of these randomly selected dogs were excluded because a CBC had not been performed during the study visit or chemotherapeutic drugs had not been administered during the visit immediately preceding the study visit; thus, there were only 77 control dogs.

Signalment and body condition—Age did not differ significantly ($P = 0.525$) between case (septic) dogs (mean ± SD, 8.1 ± 3.0 years) and control dogs (8.5 ± 3.2 years). In addition, case and control dogs did not

differ significantly with regard to sex (P = 0.470) or body condition (P = 1.000). However, case dogs had a significantly (P = 0.018) lower body weight (range, 3.6 to 55.5 kg [7.9 to 122.1 lb]; median, 23.5 kg [51.7 lb]) than did the control dogs (range, 4.4 to 77.0 kg [9.7 to 169.4 lb]; median, 29.0 kg [63.8 lb]). Further analysis of the case dogs revealed that dogs with solid tumors weighed considerably less (range, 6.8 to 40.0 kg [15.0 to 88.0 lb]; mean, 13.5 kg [29.7 lb]) than did dogs with lymphoma (range, 3.6 to 55.0 kg [7.9 to 121.0 lb]; mean, 25.3 kg [55.7 lb]); however, these values did not differ significantly (P = 0.060). In comparison, body weight for control dogs with lymphoma ranged from 8.0 to 77.0 kg (17.6 to 169.4 lb), with a median of 28.5 kg (62.7 lb), whereas body weight for control dogs with solid tumors ranged from 4.5 to 67.0 kg (9.9 to 147.4 lb), with a median of 30 kg (66.0 lb); however, these values also did not differ significantly (P = 0.771). Rottweilers were significantly (P = 0.036) less likely to be septic than were dogs of any of other breed.

Tumor type and stage—Case dogs were significantly (P = 0.037) more likely to have a lymphoma than a solid tumor (26/39 [66.7%] dogs), compared with control dogs (35/77 [45.5%]; **Table 1**). There was a significant (P = 0.014) association between being a case dog (ie, developing sepsis) and having lymphoma. However, when the effect of body weight and tumor type was analyzed in a logistic regression model, tumor type was not significantly (P = 0.071) associated, but body weight was significantly associated (OR = 0.96; 95% CI, 0.93 to 0.99; P = 0.013). There were no significant differences between case and control dogs regarding stage of disease (stage V vs stages I to IV for lymphoma or leukemia), metastasis (solid tumors), or remission status (lymphoma or leukemia).

Treatment factors—The chemotherapeutic drug used was significantly associated with the risk for development of sepsis. The chemotherapeutic drugs used (alone or in combination) included doxorubicin

Table 1—Summary of selected risk factors for the development of sepsis evaluated for 39 septic (case) dogs and 77 nonseptic (control) dogs undergoing chemotherapy.

	Control dogs (n = 77)		Case dogs (n = 39)	
Variable	**No.**	**%**	**No.**	**%**
Sex (P = 0.470)				
Sexually intact females	1	1.3	2	5.1
Spayed females	35	45.5	19	48.7
Sexually intact males	0	0	0	0
Castrated males	41	53.2	18	46.2
Body condition (P = 1.000)				
Overweight or normal weight	67	87.0	34	87.1
Underweight or cachectic	10	13.0	5	12.9
Tumor type (P = 0.037)				
Lymphoma	35	45.5	26	66.7
Leukemia	4	5.2	3	7.7
Solid tumor	38	49.4	10	25.6
Stage of lymphoma or leukemia (P = 0.447)				
I to IV	22	61.1	15	51.7
V	14	38.9	14	48.3
Metastasis of solid tumor (P = 0.414)				
No	27	71.1	9	90.0
Yes	11	28.9	1	10.0
Remission of all tumors (P = 0.457)				
No	47	61.0	21	53.8
Yes	30	39.0	18	46.2
Treatment protocol (P = 0.206)				
Single chemotherapeutic agent	58	75.3	25	64.1
Combination of chemotherapeutic agents	19	24.7	14	35.9
Dose modification or reduction (P = 0.154)				
No	59	76.6	25	64.1
Yes	18	23.4	14	35.9
Use of corticosteroids (P = 0.074)				
No	47	61.0	17	43.6
Yes	30	39.0	22	56.4
Treatment phase for lymphoma or leukemia (P = 0.070)				
Induction	18	46.2	21	72.4
Maintenance	9	23.1	2	6.9
Rescue	12	30.8	6	20.7
Drug given for the first time (P = 0.847)				
No	37	48.1	18	46.2
Yes	40	51.9	21	53.8

Table 2—Risk for development of sepsis in 39 case dogs and 77 control dogs on the basis of the chemotherapeutic drug administered.

Drug	OR*	95% CI	*P* value
Doxorubicin	12.5	2.40–66.00	< 0.001
Vincristine	9.0	1.60–52.00	0.014
Cyclophosphamide	0.6	0.04–7.10	0.652
Other drugs†	0.7	0.30–1.60	0.406

*The ORs were developed by use of multiple logistic regression and represent the OR adjusted for the other drugs and tumor type. This model had an overall $P < 0.001$. †Other drugs included carboplatin, chlorambucil, vinblastine, lomustine, mechlorethamine, fluorouracil, L-asparaginase, cisplatin, actinomycin, and methotrexate; carboplatin was removed from the model because of colinearity.

(n = 30 dogs), vincristine (21), carboplatin (18), cyclophosphamide (13), chlorambucil (6), vinblastine (6), lomustine (5), mechlorethamine (5), fluorouracil (4), L-asparaginase (3), cisplatin (3), actinomycin (1), and methotrexate (1). Logistic regression analysis (including the effect of chemotherapeutic drug and tumor type) revealed that both doxorubicin (OR = 12.5; $P < 0.001$) and vincristine (OR = 9.0; $P = 0.014$) were associated with a significantly higher risk for development of sepsis, independent of tumor type (**Table 2**). Of the 39 case dogs, 19 (48.7%) received doxorubicin prior to becoming septic, whereas only 11 (14.3%) control dogs received doxorubicin; these values differed significantly ($P < 0.001$). Similarly, 12 (30.8%) case dogs received vincristine, which differed significantly ($P = 0.014$), compared with the 9 (11.7%) control dogs that received vincristine. Among the case dogs, 12 of 26 dogs with lymphoma received doxorubicin prior to becoming septic, whereas 10 received vincristine prior to becoming septic. There were no significant differences between case and control dogs with regard to the use of a single chemotherapeutic agent versus a combination of chemotherapeutic agents or for the frequency of dose reductions (Table 1). Of the 39 case dogs, 28 (71.8%) were in the induction phase of chemotherapy, compared with 36 (46.8%) of the control dogs that were in the introduction phase; however, these values did not differ significantly ($P = 0.070$). Of the case dogs, 22 of 39 (56.4%) received concurrent corticosteroid treatment, which was not significantly ($P = 0.074$) different when compared with 30 of 77 (39.0%) control dogs that received concurrent corticosteroid treatment.

Outcome—Overall median survival time did not differ significantly ($P = 0.226$) between case (septic) dogs (median, 253 days; 95% CI, 132 to 411 days) and control dogs (median, 371 days; 95% CI, 263 to 487 days). At the conclusion of the study, 30 of 39 case dogs had died, and 9 were still alive or lost to follow-up monitoring, whereas 59 of 77 control dogs had died, and 18 were alive or lost to follow-up monitoring. In the subgroup of dogs with lymphoma, the median survival time did not differ significantly ($P = 0.317$) for 26 case and 35 control dogs (400 and 399 days, respectively; **Figure 1**). Median survival time for 10 case dogs with solid tumors was 189 days, which did not differ significantly ($P = 0.910$) from the median survival time for 38 control dogs (324 days).

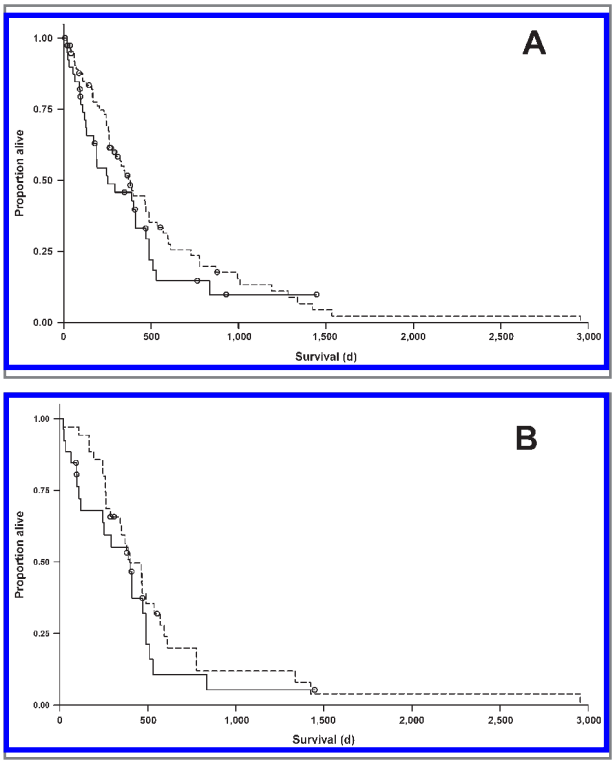

Figure 1—Kaplan-Meier survival curves for 39 septic (case) dogs and 77 nonseptic (control) dogs (A) and for 26 case dogs with lymphoma and 35 control dogs with lymphoma (B). Survival time was calculated from the date of surgery or initiation of chemotherapy to the date of death or last known status. In both portions of the figure, data for the case dogs are indicated by a solid line, and data for the control dogs are indicated by a dashed line.

Discussion

In the study reported here, risk factors for the development of sepsis in dogs receiving chemotherapy were evaluated. Other studies[4–9] have revealed that body weight is a risk factor for the adverse effects of chemotherapy in general (small dogs are more likely to develop toxic effects than are large dogs). Similarly, in our study, septic dogs weighed significantly less than did the nonseptic control dogs. There was no difference between the groups when evaluating body condition. Rottweilers were at a decreased risk for development of sepsis, probably because they were the largest breed of dog in the study and not because of an inherent resistance to sepsis. The results of this study are similar to those of other studies[5,7,8] and confirm that the current practice of administration of chemotherapeutic drugs on the basis of BSA is imperfect and may lead to relative overdosing of small animals or underdosing of large animals. Administration of chemotherapeutic drugs is based on BSA rather than on body weight because BSA is believed to correlate better with physiologic variables such as cardiac output and energy expenditure, which therefore results in more predictable and repeatable drug concentrations. However, many chemotherapeutic drugs are metabolized and excreted by the liver or kidneys, and the relationship between BSA and hepatic and renal function can be unpredictable and inconsistent. Most dogs with cancer are middle-aged or older, and they may have changes in liver and renal function that impair drug excretion and impact drug pharmacokinetics. Furthermore,

there can be extreme differences in size, shape, and conformation between dogs of different breeds, which is not taken into account by the BSA conversion formula.[4,6,9–11]

One of the most important findings in the study reported here was that tumor type was associated with an increased risk for development of sepsis. Specifically, dogs with lymphoma were significantly ($P = 0.037$) more likely to become septic than were dogs with solid tumors (66.7% vs 45.5%, respectively). This finding is even more important in light of the fact that dogs with lymphoma in the sepsis group typically were larger (but not significantly [$P = 0.060$] so) than were dogs with solid tumors in the sepsis group (median body weight, 25.3 kg vs 13.5 kg, respectively); this larger size might be thought to provide some protection against sepsis. These results may seem like a contradiction because the difference in body weight between all case dogs and all control dogs was less dramatic (range, 3.6 to 55 kg, and median, 23.5 kg [case dogs]; range, 4.4 to 77 kg, and median, 29.0 kg [control dogs]), yet these values differed significantly ($P = 0.018$). The lack of a significant difference between body weights for the subgroups of septic dogs was likely attributable to insufficient statistical power resulting from a small sample size. When evaluating the effect of body weight and tumor type in a multiple regression analysis, we determined that tumor type was not a significant ($P = 0.071$) independent risk factor for the development of sepsis but was associated with body weight; thus, an increase in body weight may confer some resistance to development of sepsis, even in dogs with lymphoma. It is possible that dogs with lymphoma are inherently more immunosuppressed than are dogs with solid tumors and that this defective or compromised immune response may make them particularly vulnerable to chemotherapy-induced myelosuppression that could result in a higher incidence of sepsis. This may explain, in part, the high incidence of sepsis early during treatment before remission has been achieved. In 1 study,[12] investigators found that untreated dogs with lymphoma and osteosarcoma have significantly fewer CD4+ T cells and CD8+ T cells than do healthy dogs. In another study,[13] investigators found that 25% of dogs with lymphoma had relative lymphopenia, compared with lymphocyte counts for clinically normal dogs. These differences may contribute to an increased susceptibility for the development of sepsis in dogs with lymphoma. However, it is interesting that the same immunologic changes were detected in dogs with osteosarcoma.[12] Despite these immunologic similarities, dogs with solid tumors (including osteosarcomas) had a decreased risk for development of sepsis in our study. This may have been attributable, in part, to the fact that dogs with osteosarcoma are typically larger dogs that may be less likely to become septic than are small dogs. These results are similar to reports[2,14–17] for humans in which patients with certain types of leukemia and lymphoma are more likely to become septic than are patients with solid tumors.

Doxorubicin and vincristine were overrepresented in the septic dogs. It is probably not unexpected that doxorubicin was the drug most often associated with development of sepsis. Many of the septic dogs with lymphoma had received doxorubicin. However, the high incidence of neutropenia and fever after administration of vincristine was a surprise. Vincristine is most often used to treat dogs with lymphoma and leukemia at our institution and is rarely used in treatment protocols for dogs with solid tumors. Our protocol for treatment of dogs with lymphoma does not include concurrent administration of L-asparaginase and vincristine, a combination that can result in severe neutropenia.[18] It is plausible that inherent immunosuppression as a result of lymphoma makes these dogs more likely to become septic. Nevertheless, the contribution of the effect of the chemotherapeutic drug to the risk of becoming septic should not be underestimated. In addition, there was typically greater use of corticosteroids in the septic dogs (56.4%), compared with corticosteroid use in the control dogs (38.9%), although these values did not differ significantly ($P = 0.074$). Corticosteroids are often administered to dogs with lymphoma during the induction phase and as part of rescue protocols but are not routinely administered to dogs with solid tumors.

The majority (21/29 [72.4%]) of the case dogs with lymphoma or leukemia were in the induction phase of chemotherapy when they became septic, compared with 18 of 39 (46.2%) of the control dogs that were in the induction phase at the time they became septic; however, these proportions did not differ significantly ($P = 0.070$). A higher incidence of sepsis might be expected the first time that a patient receives a particular drug. Patients that have neutropenia, fever, or other serious adverse effects as a result of chemotherapy early during the treatment protocol often receive reduced doses in subsequent treatments, which theoretically reduces the risk of further episodes of sepsis. However, we detected no difference between the rates for first-time drug administration in case dogs (21/39 [53.8%]) versus control dogs (40/77 [51.9%]). The lack of significant differences for these particular variables may have been attributable to the selection criteria used for the control dogs. To qualify for inclusion in the control group, dogs must have had chemotherapy administered during the preceding hospital visit. The original control population consisted of 120 dogs, but 43 dogs were excluded because the particular visit randomly chosen for comparison did not include a CBC or the dog did not receive chemotherapy at the preceding visit. Most of these excluded control dogs were receiving chemotherapy at extended intervals (maintenance) or had completed their chemotherapy treatment and were therefore not included in this study. This may inadvertently have made the control dogs more similar to the case dogs and thus biased the study toward the null hypothesis.

Most of the case dogs included in this study were treated before our institution changed to a shorter, dose-intense protocol for treatment of dogs with lymphoma. Prior to this change, dogs with lymphoma were treated by use of a cyclic sequential protocol that consisted of a sequence of 5 chemotherapeutic drugs weekly for 16 to 20 weeks before instituting an extended treatment interval. Therefore, the typical dog with lymphoma received each of the chemotherapeutic drugs several times during the first 6 months of treatment. In light of these facts, it is particularly interesting that > 50% of the dogs became septic after receiving the drug for the first time and > 70% were in the induction phase when they became septic.

Furthermore, we found that debilitated dogs with poor body condition and advanced disease that were receiving rescue chemotherapy were not at an increased risk for development of sepsis. This may have been attributable to changes in the treatment approach and goals for each specific patient over time. Most veterinary oncologists are reluctant to pursue aggressive high-dose chemotherapy in patients that have failed to have complete remission after administration of other protocols and therefore are not likely to benefit from further treatments. These factors may explain the relatively low incidence of sepsis in the dogs during the later phases of treatment.

In humans, patients with solid tumors who develop sepsis are more likely to have an uncomplicated recovery.[19–21] We found that most dogs recovered uneventfully from sepsis and continued receiving the inciting drug (with standard dose reductions) for the remainder of their treatment. Despite these dose reductions and the subsequent decrease in dose intensity, which in theory should result in decreased chemotherapy effectiveness, we did not detect significant differences between case and control dogs with regard to overall survival, either when analyzed as the entire group or analyzed as subgroups (ie, dogs with lymphoma vs dogs with solid tumors). Median survival in dogs with lymphoma was almost identical between case and control dogs (400 days vs 399 days, respectively). These results may support the practice of performing dose reductions in dogs with lymphoma that have become septic as a result of chemotherapy because survival time does not appear to be adversely affected. Case dogs with solid tumors had a shorter median survival time than did the control dogs (189 days vs 324 days, respectively). Despite this pronounced difference in the survival time, these values did not differ significantly. This lack of a significant difference may have been attributable to a lack of power (only 10 septic dogs had solid tumors) and wide CIs.

In fact, it is possible that dose reductions are more likely to adversely affect response in septic dogs with solid tumors. Solid tumors are generally not as susceptible to chemotherapy as are lymphomas; therefore, it may be more important to administer the highest possible dose to maintain efficacy. Furthermore, protocols for the treatment of solid tumors consist of fewer drugs (1 or 2 chemotherapeutic drugs) than do protocols for the treatment of lymphomas (4 or 5 chemotherapeutic drugs); therefore, a reduction of 1 drug is likely to have greater impact on the total intensity of the dose of the entire protocol.

This was a retrospective case-control study; therefore, there were inherent limitations. A larger study may have detected additional significant differences. The case dogs were identified by searching the medical records for dogs hospitalized and treated by IV administration of fluids, which was part of the standard of care for treatment of septic animals at our veterinary hospital. It is possible that some dogs with sepsis as a result of chemotherapy may not have been identified by use of this search strategy, including dogs that were treated by their referring veterinarian because of sepsis or dogs whose owners elected not to pursue treatment. However, most of the dogs treated by the veterinary oncologists at our veterinary hospital are returned to our facility for treatment if serious toxicoses develop. Similarly, most dogs with sepsis recover with appropriate care; therefore, treatment is encouraged, and most owners opt for treatment of their pets. Therefore, although some dogs with chemotherapy-induced sepsis may not have been identified by use of this search strategy, it is likely that there were only a few, and it is unlikely that they differed substantially from the case population included in the study.

The choice of a control population is always problematic in case-control studies. Choosing a control population that shares a specific characteristic or predisposing event (ie, receiving chemotherapy) with the case population may result in case and control populations that appear similar. In addition, several of the control dogs were excluded because the selected visit did not contain the information needed to answer some of our questions specifically related to the chemotherapeutic drugs; therefore, we may have inadvertently exacerbated the similarities between the case and control dogs.

Despite the potential bias toward the null hypothesis by our selection of the control dogs, we found several clinically important differences between the case and control dogs. Septic (case) dogs weighed less than did control dogs, were more likely to have lymphoma than were control dogs, and were more likely to have received doxorubicin and vincristine. In addition, most of the septic events happened early during treatment (induction phase) but did not appear to have an adverse effect on survival. These facts provide valuable practical information regarding recognition and prediction of dogs that may be at increased risk for becoming septic so that appropriate preventive measures may be instituted.

Prophylactic administration of antimicrobials may be considered in such patients, and their use has been effective in preventing hospitalization for treatment of chemotherapy-induced toxicoses in veterinary[22] and human[23–25] patients. The effectiveness of prophylactic administration of antimicrobials (ie, TMS) was evaluated in dogs with lymphoma and osteosarcoma that were receiving doxorubicin.[22] In that study, a significant decrease was detected in the rate of hospitalization and gastrointestinal toxicoses in dogs that were randomly assigned to receive prophylactically administered antimicrobials; specifically, 1 of 36 dogs receiving prophylactic TMS, versus 7 of 37 dogs receiving a placebo ($P = 0.03$), needed hospitalization. The median duration of hospitalization in this particular study was 2 days (range, 1 to 6). None of the dogs receiving TMS were hospitalized because of sepsis, whereas 5% of dogs in the placebo group were hospitalized because of neutropenia and fever; however, these proportions did not differ significantly. Because sepsis secondary to chemotherapy-induced neutropenia is relatively rare in veterinary medicine, additional studies with greater power (larger numbers of dogs from high-risk categories) may be needed to determine whether prophylactic administration of antimicrobials will be effective in preventing sepsis in this particular population.

Prophylactic administration of antimicrobials in high-risk human cancer patients can be effective in preventing hospitalization because of sepsis.[23–25] Ideally, the question of whether to routinely institute prophylactic administration of antimicrobials for small dogs with lymphoma the first time the dog receives doxorubicin or vincristine would best be answered by a prospective randomized interventional trial. However, the fact that prophylactic use of TMS significantly reduced hospitalization and the incidence or severity of gastrointestinal toxicoses in another study[22] may suggest a role for prophylactic administration of antimicrobials early during the treatment of these patients for reasons other than prevention of sepsis.

a. Stata 8.0 for Windows, StataCorp, College Station, Tex.

References

1. Chun R, Garrett L, Vail D. Cancer chemotherapy. In: *Small animal clinical oncology*. 4th ed. Philadelphia: Saunders, 2007;163–192.
2. Pizzo PA, Young RC. Infection in the cancer patient. In: DeVita VT, Hellman S, Rosenberg SA, eds. *Cancer principles and practice of oncology*. 2nd ed. Philadelphia: JB Lippincott Co, 1985;1963–1999.
3. Aschengrau A, Seage G III. Case-control studies. In: Aschengrau A, Seage G, eds. *Essentials of epidemiology in public health*. 2nd ed. Sudbury, Mass: Jones and Bartlett Publishers, 2007;229–258,
4. Arrington KA, Legendre AM, Tabeling GS, et al. Comparison of body surface area-based and weight-based dosage protocols for doxorubicin administration in dogs. *Am J Vet Res* 1994;55:1587–1592.

5. Ogilvie GK, Richardson RC, Curtis CR, et al. Acute and short-term toxicoses associated with the administration of doxorubicin to dogs with malignant tumors. *J Am Vet Med Assoc* 1989;195:1584–1587.
6. Price GS, Frazier DL. Use of body surface area (BSA)-based dosages to calculate chemotherapeutic drug dose in dogs. Potential problems with the current BSA formulae. *J Vet Intern Med* 1998;12:267–271.
7. Ogilvie GK, Moore AS, Curtis CR. Evaluation of cisplatin-induced emesis in dogs with malignant neoplasia: 115 cases (1984–1987). *J Am Vet Med Assoc* 1989;195:1399–1403.
8. Page RL, Macy DW, Thrall DE, et al. Unexpected toxicity associated with the use of body surface area for dosing melphalan in the dog. *Cancer Res* 1988;48:288–290.
9. Frazier DL, Price GS. Use of body surface area to calculate chemotherapeutic drug dose in dogs: II. Limitations imposed by pharmacokinetic factors. *J Vet Intern Med* 1998;12:272–278.
10. Sawyer M, Ratain MJ. Body surface area as a determinant of pharmacokinetics and drug dosing. *Invest New Drugs* 2001;19:171–177.
11. Baker SD, Verweij J, Rowinsky EK, et al. Role of body surface area in dosing of investigational anticancer agents in adults, 1991–2001. *J Natl Cancer Inst* 2002;94:1883–1888.
12. Walter CU, Biller BJ, Lana SE, et al. Effects of chemotherapy on immune responses in dogs with cancer. *J Vet Intern Med* 2006;20:342–347.
13. Miniscalco B, Guglielmino R, Morello E, et al. Clinical usefulness of peripheral blood lymphocyte subsets in canine lymphoma. *Vet Res Commun* 2003;27(suppl 1):407–409.
14. Hughes WT, Armstrong D, Bodey GP, et al. 2002 guidelines for the use of antimicrobial agents in neutropenic patients with cancer. *Clin Infect Dis* 2002;34:730–748.
15. Crockaert F. Febrile neutropenia in children. *Int J Antimicrob Agents* 2000;16:173–176.
16. Ohe Y, Yamamoto S, Suzuki K, et al. Risk factors of treatment related death in chemotherapy and thoracic radiotherapy for lung cancer. *Eur J Cancer* 2001;37:54–63.
17. Hamalainen S, Kuittinen T, Matinlauni I. Neutropenic fever and severe sepsis in adult acute myeloid leukemia (AML) patients receiving intensive chemotherapy: causes and consequences. *Leuk Lymphoma* 2008;49:495–501.
18. Northrup NC, Rassnick KM, Snyder LA, et al. Neutropenia associated with vincristine and L-asparaginase induction chemotherapy for canine lymphoma. *J Vet Intern Med* 2002;16:570–575.
19. Klastersky J, Paesmans M, Rubenstein EB, et al. The Multinational Association for Supportive Care in Cancer risk index: a multinational scoring system for identifying low-risk febrile neutropenic cancer patients. *J Clin Oncol* 2000;18:3038–3051.
20. Elting LS, Rubenstein EB, Rolston KVI, et al. Outcome of bacteremia in patients with cancer and neutropenia: observations from two decades of epidemiological and clinical trials. *Clin Infect Dis* 1997;25:247–259.
21. Raad II, Escalante C, Hachem RY. Treatment of febrile neutropenic patients with cancer who require hospitalization: a prospective randomized study comparing imipenem and cefepime. *Cancer* 2003;98:1039–1047.
22. Chretin JD, Rassnick KM, Shaw NA, et al. Prophylactic trimethoprim-sulfadiazine during chemotherapy in dogs with lymphoma and osteosarcoma: a double-blind, placebo-controlled study. *J Vet Intern Med* 2007;21:141–148.
23. Bucaneve G, Micozzi A, Menichetti F. Levofloxacin to prevent bacterial infection in patients with cancer and neutropenia. *N Engl J Med* 2005;353:977–987.
24. Cullen M, Steven N, Billingham L. Antibacterial prophylaxis after chemotherapy for solid tumors and lymphomas. *N Engl J Med* 2005;353:988–998.
25. Kurt B, Flynn P, Shenep JL. Prophylactic antibiotics reduce morbidity due to septicemia during intensive treatment for pediatric acute myeloid leukemia. *Cancer* 2008;113:376–382.