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Adjuvant carboplatin for treatment of splenic hemangiosarcoma in dogs: Retrospective evaluation of 18 cases (2011-2016) and comparison with doxorubicin-based chemotherapy

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Abstract

Background: Doxorubicin-based chemotherapy after splenectomy remains the standard of care for hemangiosarcoma in dogs, but prognosis is generally poor.

Hypothesis/objectives: To determine clinical outcome with carboplatin chemotherapy after splenectomy compared to doxorubicin-based protocols. A secondary objective was to determine if peripheral monocyte count was associated with prognosis.

Animals: Medical data from 40 dogs with histopathologically confirmed stage I or II hemangiosarcoma treated with splenectomy and carboplatin (n = 18) or doxorubicin-based protocols (n = 22) were evaluated.

Methods: Retrospective study. Statistical associations were assessed using the Kaplan-Meier method for survival times and log rank analysis for differences in survival time. Demographic information and survival times were obtained via medical records. Blood monocyte counts before and after surgery were documented.

Results: Median survival times were 160 days (48 to >559) and 139 days (54-975), for dogs in the carboplatin (n = 18) and doxorubicin (n = 22) groups respectively ($P = .82$, hazards ratio [HR] [95% CI] = 1.075 [0.56-2.07]). The median survival time for dogs whose monocyte counts decreased between splenectomy and chemotherapy initiation was 265 days, compared to 66 days for dogs with increased monocytes ($P = .002$, HR [95% CI] = 4.17 [1.21-14.39]).

Conclusions and Clinical Importance: Carboplatin could be considered as an alternative in cases where doxorubicin might be contraindicated. Increasing postoperative peripheral monocyte counts might be associated with a poorer prognosis.

KEYWORDS
cancer, chemotherapy, dog, monocytes, spleen

Abbreviations: DOX, doxorubicin; HSA, hemangiosarcoma; MC, metronomic chemotherapy; MST, median survival time; OSA, osteosarcoma.

1 | INTRODUCTION

Hemangiosarcoma (HSA) accounts for 45% to 51% of all splenic malignancies and is the most common cause of nontraumatic hemoabdomen in dogs. Splenectomy is the initial treatment of choice, but because of the aggressive biologic behavior of HSA, the median survival time (MST) with surgery alone is less than 3 months (42-86 days).[1,2] Adjuvant chemotherapy with doxorubicin (DOX)-based protocols is the current standard of care, with MSTs of 141 to 179 days in multiple independent studies.[3-7] Alternate therapies, including metronomic chemotherapy (MC) protocols with cyclophosphamide, etoposide, and immunotherapies, have been attempted without much evidence for improved survival times.[8-12] Despite the addition of these therapies, 1-year survival percentages remain less than 16% for dogs with stage II or III disease.[13] Because of poor prognoses, studies evaluating alternate therapeutic options for this highly aggressive disease continue to be of interest to the veterinary oncology field.

Doxorubicin is the drug typically used to treat humans and dogs with HSA because of its potent anticancer effects in humans and dogs[4,13]; but, DOX can cause dose-dependent cumulative cardiotoxicosis, which precludes its use in some dogs.

Carboplatin has similar mechanism of action and spectrum of efficacy compared to cisplatin, but without the dose-limiting nephrotoxicity, severe emetogenic properties, or pulmonary edema observed in cats.[14] Because of improved safety and comparative efficacy, it has been the most utilized platinum drug in veterinary medicine. It is most commonly used as an adjuvant treatment for osteosarcoma (OSA) in dogs,[15,16] as well as in a variety of carcinomas including transitional cell carcinoma,[17,18] squamous cell carcinoma,[19] anal sac adenocarcinoma,[20] and oral malignant melanoma.[21,22]

Monocytes and macrophages play a key role in promoting tumor metastasis in humans and rodents.[23,24] Studies in dogs revealed that higher pretreatment circulating monocytes are associated with a poorer prognosis in dogs with OSA and lymphoma.[25,26] Hemangiosarcoma pulmonary metastases have significantly higher macrophage densities compared with that in tissue of many other canine tumor types.[27]

In this study, we sought to compare the survival times of dogs treated with adjuvant carboplatin chemotherapy with dogs that received DOX-based regimens. As an additional aim, we evaluated monocyte counts in a subset of dogs to determine if a correlation existed between peripheral blood monocytes and overall survival.

2 | MATERIALS AND METHODS

2.1 | Case selection criteria

Medical records at the Colorado State University (CSU) Veterinary Teaching Hospital were searched to identify dogs diagnosed with primary splenic HSA between January 2011 and April 2016. Dogs were included in the study if they had undergone a splenectomy at either the referring veterinarian or CSU, had histopathologic confirmation of splenic HSA, and were clinically staged as stage I or II. Dogs included in the study must have had received ≥1 IV dose of chemotherapy as part of a single-agent carboplatin or a DOX-based protocol, postoperatively. Clinical staging consisted of 3-view thoracic radiographs, and either abdominal ultrasound or abdominal exploratory surgery within 21 days of chemotherapy initiation. Echocardiography was performed at clinician discretion.

Dogs were excluded from the study if they had evidence of gross metastatic disease, including liver or omental metastasis at the time of surgery, cardiac involvement based on echocardiography, or lung metastasis based on radiographs. For both groups, dogs that received any other antineoplastic drugs or continuous MC after completing the MTD protocols were also excluded.

2.2 | Data collection

This was a single-center, retrospective cohort study. Data abstracted from the medical records included dog breed, sex, neuter status, and age at diagnosis. Tumor stage was determined based on the presence of hemoabdomen, surgical reports, and results of imaging tests (thoracic radiographs, abdominal ultrasound, and echocardiogram) performed preoperatively or before initiating chemotherapy. The date of diagnosis, chemotherapy start date, date of death and, when known, cause of death were obtained from CSU records or primary care veterinarians. When available, preoperative monocyte counts were recorded. Postoperative monocyte counts were obtained for all before, usually from the complete blood counts obtained before chemotherapy was instituted.

Because numbers were low in the DOX group obtained from 2011 to 2016, we added data from earlier noncontemporaneous dogs for the analysis. We added 16 dogs of various breeds with stage I or II HSA that had been treated with DOX alone or a combination of DOX and cyclophosphamide, which brought the total number of dogs to 22 in the DOX group.

2.3 | Statistical analysis

For comparing demographic factors and monocyte numbers between groups, a 2-tailed, unpaired Mann-Whitney test was used for continuous variables and a 2-tailed Fisher exact test for categoric variables. The Kaplan-Meier method was utilized to estimate and display survival times, and differences in overall survival time between groups was compared using log-rank analysis. Factors evaluated for potential prognostic value included age, sex, body weight, clinical stage, presurgical/prechemotherapy monocyte count, treatment group, and pre/postsurgical change in monocyte counts. For evaluation of pre/post change in monocyte count, dogs were dichotomized into those with a postoperative decrease and those with an increase and these groups compared via log-rank analysis. Prism 8 software (GraphPad, La Jolla, California) was used in all statistical analyses.

3 | RESULTS

3.1 | Animals

A total of 40 dogs were included in the study and were divided into 2 groups for the comparison studies. The carboplatin group (n = 18) received a single-agent carboplatin regimen. The DOX group (n = 22) included 6 dogs receiving single agent DOX and 16 dogs receiving DOX and cyclophosphamide. The median number of carboplatin doses administered was 3.5 (1-6) and the median number of DOX doses administered was 4 (3-5). The median starting carboplatin dose was 300 mg/m^2 (240-300 mg/m^2) and the median DOX dose was 30 mg/m^2 (22-30 mg/m^2). One dog weighing less than 15 kg received a DOX dose of 1 mg/kg. Characteristics and descriptive statistics for these animal groups are provided in Table 1.

The groups were balanced for most factors. The carboplatin group had significantly more Labrador Retrievers and the DOX group had significantly more mixed breed dogs.

3.2 | Survival analyses

The survival times of dogs treated with either DOX or carboplatin are depicted in Figure 1. One dog in each group was alive at the time of last follow-up (732 and 559 days). All dogs in the carboplatin group (n = 18) and 19 of 22 dogs in the DOX group died as a result of HSA progression. The MST of the dogs in the carboplatin group (n = 18) was 160 days. The DOX group (n = 22) had a MST of 139 days, with no significant difference between those dogs receiving cyclophosphamide and those receiving DOX only (not shown). There was no significant difference observed between the carboplatin and DOX groups (P = .82, hazards ratio [HR] [95% CI] = 1.075 [0.56-2.07]; Figure 1A).

We then compared outcomes in DOX vs carboplatin treated dogs when stratified by stage (Figure 1B,C). There was no difference in outcome between carboplatin and DOX for dogs with stage I (MST 341.5 vs 207 days respectively, P = .11, HR [95% CI] = 1.20 [0.36-4.00]) or stage II disease (MST 97.5 days vs 133 days respectively, P = .48, HR [95% CI] = 1.32 [0.57-3.07]). The effect of stage on outcome was then examined in the carboplatin group (Figure 2A). Dogs with stage I HSA had significantly better outcomes (MST = 341.5 days) than dogs with stage II HSA (97.5 days; P = .02, HR [95% CI] = 3.75 [1.25-11.25]). In the DOX group, there was no significant difference in outcome based on stage (P = .23, HR [95% CI] = 0.52 [0.198-1.37]; Figure 2B).

3.3 | Blood monocyte counts

Absolute preoperative or postoperative monocyte counts were not associated with outcome in this cohort, and there was no difference in postoperative monocyte counts between carboplatin and DOX treated dogs (P = .91). However, a comparison between presurgical and postsurgical (day of chemotherapy initiation) monocyte counts could be made for 10 carboplatin treated dogs (Figure S1A). The MST for dogs that had a decreased monocyte count postsplenectomy vs presplenectomy was 265 days, compared to 66 days for those dogs with an increase in peripheral monocytes (Figure 2C). This difference was statistically significant (P = .002, HR [95% CI] = 4.17 [1.21-14.39]). There were no statistical associations between pretreatment or posttreatment monocyte counts, or change in monocyte count, and clinical stage in this cohort (Figures S1B-D).

4 | DISCUSSION

Carboplatin has been used as a single agent and as adjuvant treatment for several neoplastic diseases in dogs[15-22]; however, to date, no studies have evaluated the efficacy of carboplatin for the treatment of splenic HSA. Therefore, the main aim of this study was to examine

TABLE 1 Characteristics of the 40 total dogs in the study, including age, sex, breed, and stage of disease

		Carboplatin (n = 18)	Doxorubicin (n = 22)	*P* value
Age (year)	Median (range)	8.5 (5-13)	10 (3-13)	.13
Sex	MC	13	9	.09
	MI	0	2	
	FS	5	11	
Weight (kg)	Median (range)	32.15 (7.2-50)	26.55 (18-47.3)	.42
Breed	Mixed breed	0	7	.02
	Labrador Retriever	6	1	
	Golden Retriever	5	4	
	German Shepherd	2	3	
	Boxer	2	0	
	Other (1 each)	4	7	
Stage	1	8	7	.41
	2	10	15	
# Censored	Alive	1	1	
	Died - unrelated	0	3	

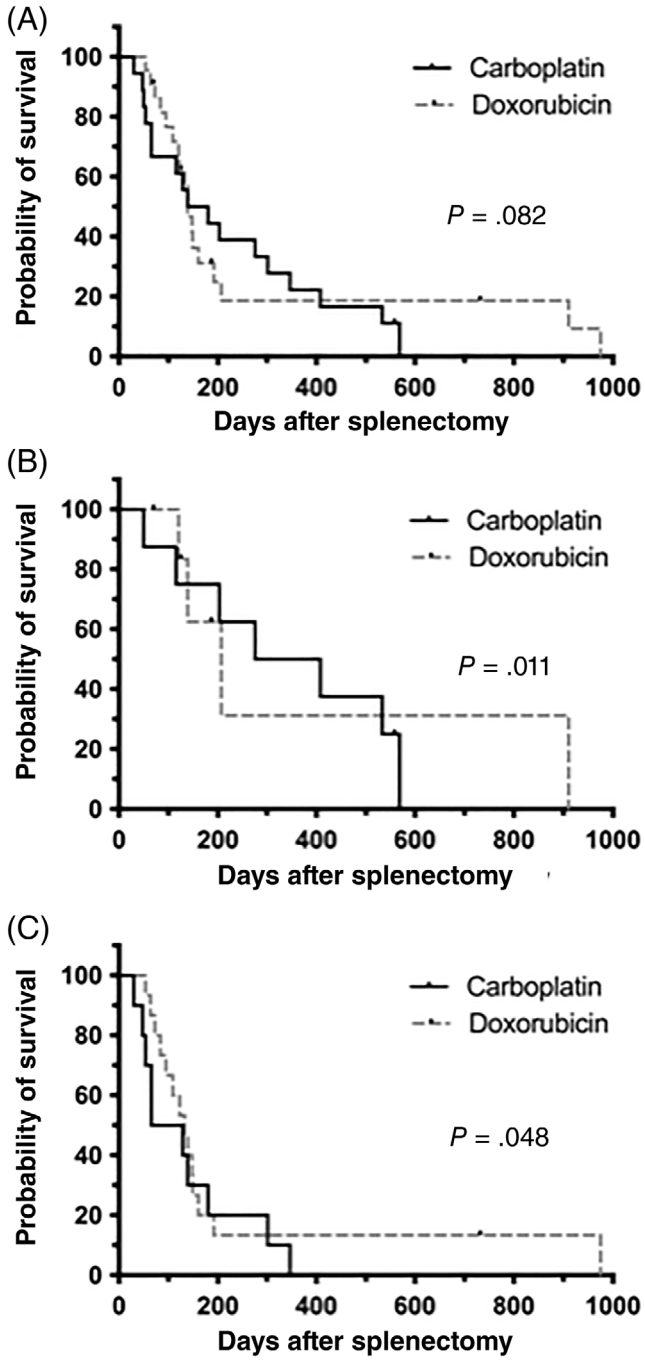

FIGURE 1 Kaplan-Meier analysis was used to estimate the survival times of dogs with splenic hemangiosarcoma that received adjuvant carboplatin or DOX-based chemotherapy. A, Entire population; B, dogs with stage I disease; C, dogs with stage II disease. There was no significant difference between the 2 chemotherapy groups for the entire population or when stratified by stage. Tick marks indicate censored dogs

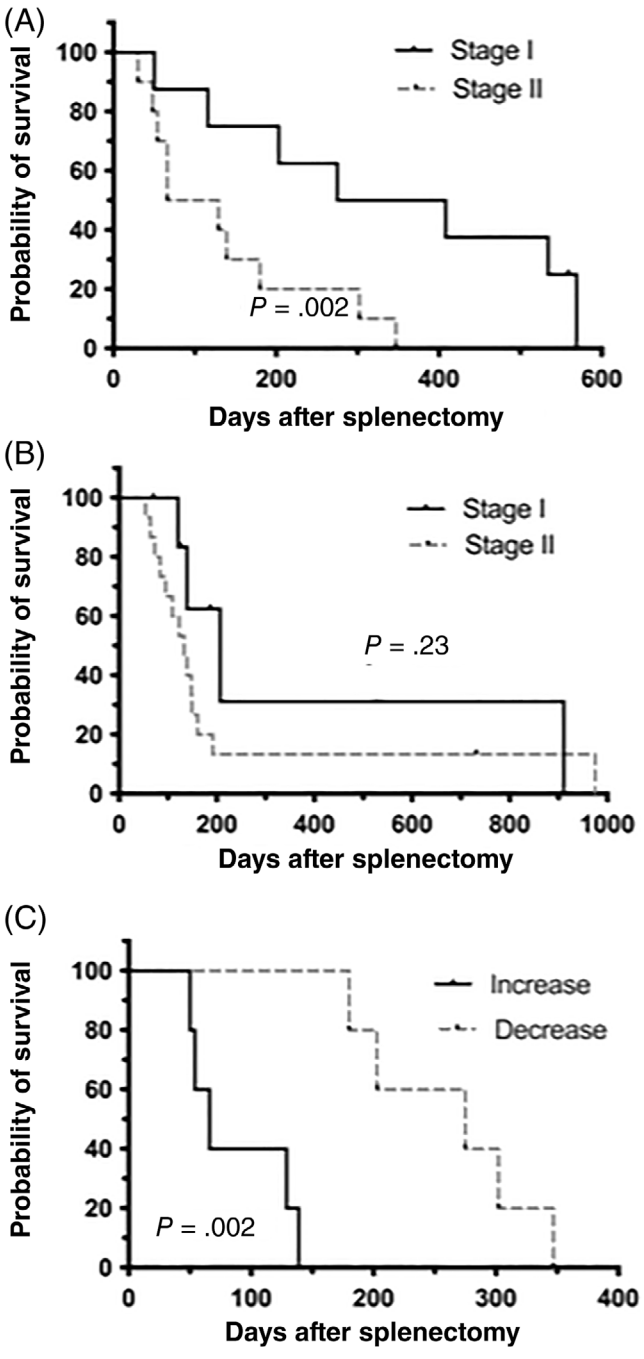

FIGURE 2 In the carboplatin group (A) there was a significant difference ($P = .02$) in median survival time (MST) of dogs with stage I HSA compared with stage II HSA, while no significant difference was observed in the dogs treated with doxorubicin (B; $P = .23$). C, The relationship between median survival time (MST) and change in peripheral monocyte counts in dogs with HSA. Dogs with decreasing postoperative monocyte counts had significantly ($P = .002$) increased MST when compared with dogs with increasing monocyte counts. Tick marks indicate censored dogs

the efficacy of single-agent carboplatin treatment for the treatment of HSA compared with that of DOX. Overall, no differences in outcome were observed between dogs treated with DOX-based treatment vs carboplatin-based treatment. This lack of a difference suggests that carboplatin might be acceptable to consider in place of DOX to treat splenic HSA with similar efficacy, which would be especially useful in dogs that are more susceptible to DOX-induced cardiotoxicity.[28] Unlike DOX, carboplatin is not a P-glycoprotein substrate and can therefore be safely used in dogs with *abcb1* gene mutations.[29] It is important to note that with a small number of cases, true equivalency

cannot be definitively confirmed as there is limited power to detect differences in outcome between groups.

Carboplatin was designed as a safer chemotherapeutic drug to its sister platinum-based drug, cisplatin.[30] It was evaluated at our institution as an adjuvant treatment after observation of a meaningful and reasonably durable objective response in a dog with measurable metastatic HSA. It has been used extensively in canine OSA but, to date, was only used once to treat HSA of the os penis in conjunction with surgery and DOX.[31] In this case, the combination of DOX and carboplatin adjuvant treatment was moderately successful as the dog survived 20 months. In a phase I clinical trial evaluating carboplatin in tumor-bearing cats, a complete response was reported in a cats with cutaneous HSA.[32]

The target number of carboplatin doses to be administered during the period of time that this treatment was being offered was 4. Indeed, 7 of 18 dogs did receive the planned 4 doses. Nine dogs received between 1 and 3 doses as a result of early disease progression leading to death/euthanasia or a change in protocol, and 1 dog each received 5 and 6 doses, at owner request. It is possible that a longer duration of treatment in those dogs not developing disease progression at the time of protocol completion could have conferred additional benefit.

Several adjuvant therapies have been investigated in an attempt to improve survival times after splenectomy for dogs with HSA. Doxorubicin, as the mainstay of adjuvant therapies, has been used as a single agent[5] and in combination with several other drugs, immunotherapy approaches, and drug delivery systems to improve upon the survival times of these dogs. A few of these combined therapies have been proposed with limited success. No significant difference was seen in the overall survival or progression-free survival of dogs with splenic HSA that received DOX alone or DOX with MC.[8] A recent prospective study showed a significant improvement in time to metastasis (TTM) and MST in dogs with HSA of any organ that received DOX plus dacarbazine compared with those that received DOX plus cyclophosphamide.[9] In another study, MC treatment was preceded by a maximum tolerated adjuvant DOX chemotherapy (MTDC) dose and was then compared with MTDC alone. Most of the dogs (10/12) received MC treatment after MTDC (MTDC-MC), and of those dogs, median TTMs and STs were significantly longer for dogs that received MTDC-MC compared with those that received MTDC only.[10] Finally, liposome encapsulation of DOX alone or in combination with other chemotherapeutic agents have shown mixed results in dogs with HSA.[3,11]

There was a significant difference in overall survival between in the dogs with stage I and stage II splenic HSA that received carboplatin adjuvant chemotherapy. We did not observe a significant difference in overall survival between the dogs with stage I and II dogs in the DOX group, however. This was surprising considering differences have been shown with DOX-based studies between dogs with the different stages of splenic HSA.[33-35]

Our interest in determining if peripheral blood monocyte counts could predict survival stemmed from 2 different studies. A study showed that an increased infiltration of $CD18^{+}$ macrophages was found preferentially in HSA compared with other tumor-types.[27] Additionally, 2 previous studies from our group found that pretreatment blood monocyte counts could predict survival in dogs with OSA and were correlated with a poor prognosis in dogs with lymphoma.[25,26] The fact that absolute preoperative or postoperative monocyte counts were not predictive of outcome, while change in monocyte counts after surgery had predictive value, has not been observed in tumor-bearing dogs previously. It is possible that an increase in peripheral monocytes postoperatively could be an indicator of high residual disease burdens or early tumor progression. This observation warrants additional investigation, especially given the very small number of dogs in this study for which this analysis was possible. Furthermore, additional interrogation of the prognostic value of presurgical monocyte counts is warranted, given the small number of samples available for analysis in this study.

Limitations to this study that include its retrospective nature and that a small number of animals were included. Additionally, clinical staging was variable between dogs, especially as it pertains to the inclusion of echocardiography. It is thus possible that a small number of dogs with occult cardiac involvement could have been included. However, the results nevertheless suggest that carboplatin was a reasonably effective drug that could be used in the place of DOX for the treatment of splenic HSA.

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CONFLICT OF INTEREST DECLARATION

Authors declare no conflict of interest.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Authors declare no IACUC or other approval was needed.

HUMAN ETHICS APPROVAL DECLARATION

Authors declare human ethics approval was not needed for this study.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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