Appendicular osteosarcoma is the most common primary bone tumor in dogs, with up to 90% of affected patients developing distant metastasis following limb amputation.\(^1\) Reported median survival time ranges from 3 to 5 months following local definitive treatment (eg, limb amputation) and can be extended to a range of 8 to 11 months with the addition of adjuvant systemic chemotherapy.\(^1\)–\(^8\)

To improve the poor prognosis associated with osteosarcoma, investigation into novel treatments is needed. Metronomic chemotherapy, defined as “the chronic administration of chemotherapeutic agents at relatively low, minimally toxic doses and with no prolonged drug-free breaks,” targets tumor angiogenesis, the suppressed immune system of cancer patients, or both.\(^9\) These combined antineoplastic mechanisms have potential clinical benefits against osteosarcoma in dogs owing to the high angiogenic capacity and modified immunologic profile of this cancer. Studies\(^10\)–\(^11\) have shown in vitro expression of the angiogenic factor VEGF by osteosarcoma cells as well as high circulating VEGF concentrations in dogs of adjuvant systemic chemotherapy.\(^1\)–\(^8\)

OBJECTIVE
To determine the effectiveness of metronomic cyclophosphamide (MC) chemotherapy (primary treatment of interest) with adjuvant meloxicam administration as maintenance treatment for dogs with appendicular osteosarcoma following limb amputation and carboplatin chemotherapy.

DESIGN
Retrospective case series with nested cohort study.

ANIMALS
39 dogs with a histologic diagnosis of appendicular osteosarcoma that underwent limb amputation and completed carboplatin chemotherapy from January 2011 through December 2015.

PROCEDURES
Dogs were grouped by whether carboplatin chemotherapy had been followed with or without MC chemotherapy (15 mg/m\(^2\), PO, q 24 h) and meloxicam (0.1 mg/kg [0.045 mg/lb], PO, q 24 h). The Breslow rank test was used to assess whether MC chemotherapy was associated with overall survival time (OST) and disease progression-free time (PFT) after limb amputation.

RESULTS
19 dogs received carboplatin and MC chemotherapy, and 20 dogs received only carboplatin chemotherapy. No differences were identified between these groups regarding age, reproductive status, body weight, serum alkaline phosphatase activity, tumor location, or histologic grade or subtype of osteosarcoma. Median duration of MC chemotherapy for dogs in the carboplatin-MC group was 94 days (range, 7 to 586 days); this treatment was discontinued for 11 (58%) dogs when cystitis developed. Overall, 11 (28%) dogs survived to the time of analysis, for a median follow-up period of 450 days (range, 204 to 1,400 days). No difference in median PFT or OST was identified between the 2 groups.

CONCLUSIONS AND CLINICAL RELEVANCE
Maintenance MC chemotherapy following limb amputation and completed carboplatin chemotherapy was associated with no increase in PFT or OST in dogs with appendicular osteosarcoma. Cystitis was common in MC-treated dogs, and prophylactic treatment such as furosemide administration could be considered to reduce the incidence of cystitis in such dogs. (J Am Vet Med Assoc 2018;252:1377–1383)
with osteosarcoma. In addition, serum VEGF concentration in dogs with osteosarcoma is correlated with disease-free interval following amputation and adjuvant chemotherapy.12 Dogs with osteosarcoma also have high numbers of circulating regulatory T cells, which can be reversed by MC administration.13,14 A decrease in the ratio of CD8 to regulatory T cells is reportedly associated with a decrease in survival time after standard treatment.13 This evidence suggests the potential benefit of metronomic chemotherapy for dogs with osteosarcoma. Indeed, clinical responses to metronomic chemotherapy have been demonstrated in small preliminary in vivo studies15-18 of osteosarcoma in humans, dogs, and rats.

A study19 of the safety of concurrent MC and MTD chemotherapy following limb amputation in dogs with osteosarcoma revealed that this treatment strategy was well tolerated, with a median postamputation survival time of 6 to 7 months. However, lack of a control group in the study precluded drawing of conclusions regarding treatment effectiveness. Another study20 revealed loss of the immunomodulatory effects of MC chemotherapy when provided concurrently with MTD doxorubicin chemotherapy.20 These findings support potential exploration of a sequential treatment approach involving MC chemotherapy following completion of MTD chemotherapy instead of concurrent treatment with these 2 approaches. In a large randomized prospective clinical trial,21 dogs with osteosarcoma were treated by MC administration with or without toceranib phosphate, and addition of toceranib phosphate failed to improve survival times; however, the impact of MC administration on prognosis is unknown.

Metronomic cyclophosphamide administration at a dose of 15 mg/m² reportedly induces a more potent inhibitory effect on regulatory T cells than administration at a lower dose of 12.5 mg/m².14 However, the impact of MC administration at 10 mg/m² daily or every other day, 12.5 mg/m² daily, and 25 mg/m² daily on the treatment response of dogs with various cancers has been investigated without concurrent immunomodulatory effects in several studies.14,17,21-24

An NSAID is often combined with cyclophosphamide as a component of metronomic chemotherapy protocols in veterinary oncology owing to the antiangiogenic effects of NSAIDs.17,22-24 At the Ontario Veterinary College Veterinary Teaching Hospital, meloxicam has been routinely used as the chosen NSAID for combination with cyclophosphamide. The aim of the study reported here was to determine the effectiveness of MC administration at 15 mg/m²/d plus meloxicam as maintenance treatment after limb amputation and completion of adjuvant carboplatin chemotherapy in dogs with appendicular osteosarcoma. We hypothesized that dogs receiving MC chemotherapy as a maintenance treatment would have a longer median survival time after limb amputation than dogs receiving no MC treatment.

Materials and Methods

Case selection criteria

Medical records of the Ontario Veterinary College Veterinary Teaching Hospital were electronically searched to identify dogs with a histologic diagnosis of appendicular osteosarcoma and no gross evidence of metastatic disease that were treated by limb amputation plus adjuvant carboplatin chemotherapy, with or without subsequent MC chemotherapy (15 mg/m², PO, q 24 h), between January 1, 2011, and December 31, 2015. Absence of metastatic disease was confirmed on the basis of results of 3-view thoracic radiography or thoracic CT with or without abdominal ultrasonography. Dogs were excluded if they lacked a histologic diagnosis, had not completed a carboplatin treatment protocol, had evidence of metastatic gross disease at the beginning of MC chemotherapy, or received MC chemotherapy at a dose or frequency other than 15 mg/m²/d.

Treatment protocol

The standard of care for dogs with appendicular osteosarcoma at the Ontario Veterinary College was forequarter limb amputation or hip joint disarticulation followed by adjuvant carboplatin treatment. Carboplatin® (300 mg/m²) was administered IV over a 10-minute period every 3 weeks, beginning 10 to 14 days after limb amputation. The total number of carboplatin doses varied from 4 to 6, depending on the treatment protocol at the time. This protocol changed from 5 doses before January 2011 and 6 doses from January 2011 to December 2015 to 4 doses thereafter. Thoracic radiographs were obtained at the time of diagnosis, between the fourth and sixth carboplatin dose, and every 3 months thereafter.

After completion of the carboplatin protocol, MC chemotherapy (15 mg/m², PO, q 24 h) was offered to the owners and initiated when elected, and meloxicam was concurrently administered (0.1 mg/kg [0.045 mg/lb], PO, q 24 h). Cyclophosphamide was compounded and prescribed through a human and veterinary compounding pharmacy on the basis of body surface area. For MC-treated dogs, recheck CBCs were performed 2 and 4 weeks after treatment began and then monthly. To reduce the risk of cyclophosphamide-induced cystitis, clients were instructed to administer cyclophosphamide in the morning and to encourage their dog to urinate by taking it outdoors more often than usual. The MC chemotherapy protocol was intended to be administered continuously until tumor progression or chemotherapy-associated adverse events were documented.

Data collection and follow-up

Data collected from the medical records included dog age, reproductive status, breed, and body weight; whether serum ALP activity was greater than the upper reference limit (reference range, 22 to 143 U/L); diagnostic imaging findings prior to amputation; amputation date; tumor location; carboplatin dose and administration dates; other chemotherapy data; MC data (dose and duration); adverse events if applicable; results of follow-up staging tests; and date and cause of death or euthanasia. Severity of chemo-
therapy-associated adverse events was graded by use of a published scoring system.25

For additional follow-up information, referring veterinarians or owners were contacted via telephone at the time of study data collection. Overall survival time was defined as the time elapsed between limb amputation and death or euthanasia due to any cause. Progression-free time was defined as the time elapsed between limb amputation and first evidence of tumor progression or death or euthanasia.

**Histologic assessment**

All available histologic slides of tumor specimens were reviewed by a veterinary pathologist (CRS) at the time of data collection to confirm the histologic diagnosis of osteosarcoma. The slides were also assessed for tumor grade and subtype as described elsewhere26 to determine whether these variables were associated with outcome.

**Statistical analysis**

Dogs were allocated to 2 groups: those treated with carboplatin followed by maintenance MC chemotherapy (carboplatin-MC group) or those treated with carboplatin only (carboplatin group). The 2 groups were compared with respect to age, reproductive status, body weight, serum ALP activity at the time of diagnosis (high or not high), tumor location, number of carboplatin doses administered, whether a carboplatin dose reduction was required (yes or no), and histologic subtype and grade of osteosarcoma. Distributions of categorical data were compared with the Fisher exact test. Continuous data (age, body weight, and number of carboplatin doses administered) were first analyzed for normality by use of the Shapiro-Wilk test, and on the basis of the results, these data were compared with the 2-sample t test (normally distributed data) or Mann-Whitney test (nonnormally distributed data).

For PFT analyses, dogs that were still alive or lost to follow-up without disease progression at the time of analysis were censored at the time of last contact. Dogs that were still alive or that were lost to follow-up at the time of the analysis were censored from the OST analysis at the time of last contact. All deaths for unknown reasons were presumed to have been related to osteosarcoma. The Kaplan-Meier method was used to calculate median PFT and OST. The Breslow test was used to compare survival curves between the 2 groups given that the survival curves crossed. Values of \( P < 0.05 \) were considered significant. All analyses were performed with the aid of statistical software.

**Results**

**Dogs**

Thirty-nine dogs met the criteria for inclusion in the study, and their characteristics were summarized (Table 1). Dogs were classified as mixed-breed dog

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Carboplatin-MC</th>
<th>Carboplatin only</th>
<th>P value</th>
</tr>
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<tr>
<td>Age (y)</td>
<td>7 (3–13)</td>
<td>8 (5–11)</td>
<td>0.19</td>
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<td>Body weight (kg)</td>
<td>38.0 (27.6–61.0)</td>
<td>40.4 (25.4–66.0)</td>
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<tr>
<td>Sexually intact female</td>
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<td>—</td>
</tr>
<tr>
<td>Spayed female</td>
<td>9 (47)</td>
<td>8 (40)</td>
<td>—</td>
</tr>
<tr>
<td>Sexually intact male</td>
<td>0 (0)</td>
<td>2 (10)</td>
<td>—</td>
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<tr>
<td>Castrated male</td>
<td>9 (47)</td>
<td>9 (45)</td>
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<tr>
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<tr>
<td>High (&gt; 143 U/L)</td>
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<td>17 (85)</td>
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</tr>
<tr>
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<td>2 (10)</td>
<td>—</td>
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<tr>
<td>Tumor location</td>
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<tr>
<td>Humerus</td>
<td>4 (21)</td>
<td>3 (15)</td>
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<tr>
<td>Radius</td>
<td>9 (47)</td>
<td>8 (40)</td>
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<td>Femur</td>
<td>3 (16)</td>
<td>6 (30)</td>
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<tr>
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<td>3 (15)</td>
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<tr>
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<td>4 (20)</td>
<td>—</td>
</tr>
</tbody>
</table>

Data are reported as median (range) for age and body weight and number (%) of dogs in category for reproductive status, serum ALP activity, and tumor location.

— = Not applicable.
(n = 8), Rottweiler (6), Greyhound (5), Golden Retriever (3), Doberman (3), Mastiff (2), Saint Bernard (2), Akita (1), Alaskan Malamute (1), Bernese Mountain Dog (1), Dogue de Bordeaux (1), German Shepherd Dog (1), Great Dane (1), Leonberger (1), Labrador Retriever (1), Newfoundland (1), and Portuguese Water Dog (1).

Nineteen dogs qualified for the carboplatin-MC group, and 20 dogs qualified for the carboplatin group. No significant differences were identified between these 2 groups regarding age, body weight, reproductive status, serum ALP activity, or tumor location (Table 1). On presurgical staging of tumors, none of the 39 dogs had evidence of pulmonary metastasis as determined via thoracic radiography (n = 38) or thoracic CT (1). Seventeen dogs also underwent abdominal ultrasonography, and 1 dog also underwent abdominal CT, and none of these 18 dogs had evidence of intra-abdominal metastasis.

**Carboplatin chemotherapy**

All 39 dogs received carboplatin as an adjuvant MTD treatment, beginning at a dose of 300 mg/m². This dose needed to be reduced for 4 dogs owing to grade III neutropenia (n = 2), grade III gastrointestinal toxic effects (1), or grade II lethargy (1). Thirty-one dogs received 4 carboplatin doses, 1 dog received 5 doses, and 7 dogs received 6 doses. No significant differences were identified between groups regarding whether a dose reduction had been required (P = 0.32) or the median number of carboplatin doses received (P = 0.92). All dogs underwent thoracic radiography at or around the time the final 2 carboplatin doses were administered, which confirmed no evidence of metastasis.

**Adjuvant meloxicam administration**

Eight (40%) dogs in the carboplatin group received meloxicam. Two dogs received meloxicam throughout the follow-up period, 3 dogs received meloxicam intermittently as needed for pain, and 3 dogs began to receive meloxicam after they developed metastatic disease. Eleven dogs in the carboplatin group did not receive meloxicam; no follow-up information regarding meloxicam administration was available for the remaining dog.

Eighteen (95%) dogs in the carboplatin-MC group also concurrently received meloxicam. One (5%) dog received firocoxib (6 mg/kg [2.7 mg/lb], PO, q 24 h) instead owing to owner preference.

**MC chemotherapy**

All 19 dogs in the carboplatin-MC group received cyclophosphamide daily at 15 mg/m², PO. Median duration of MC administration was 94 days (range, 7 to 586 days). One (5%) dog was still receiving MC treatment at the time of its final visit during the study period, and this treatment was discontinued for the remaining dogs because of cystitis (n = 11 [58%]), tumor progression (3 [16%]), signs of gastrointestinal toxic effects (2 [11%]), rupture of multiple cutaneous cysts (1 [5%]), and no reported reason (1 [5%]). The dog with multiple cutaneous cysts had a large cyst rupture prior to beginning MC treatment, and the owner discontinued MC treatment 7 days after it began because of the rupture.

Adverse effects attributed to MC treatment included grade II or III cystitis (n = 11 [58%]), grade I gastrointestinal signs (2 [11%]), and grade I lethargy (1 [5%]). In 7 of the 11 dogs with cystitis, this condition was confirmed by clinical signs and urinalysis findings of microscopic hematuria without a high leukocyte count or identifiable bacteria. In the remaining 4 dogs, cystitis was clinically suspected because of signs of stranguria with or without macroscopic hematuria not confirmed by urinalysis. For 4 of the 7 dogs that received a urinalysis, bacterial culture of urine was also performed, yielding no bacterial growth. None of the 19 dogs developed signs of hematologic toxic effects.

**Other treatments**

Palliative radiation therapy (2 × 10 Gy) for the primary osteosarcoma lesion and pamidronate disodium infusion (1 to 2 mg/kg [0.45 to 0.9 mg/lb], IV, over a 2-hour period, q 28 d) were provided to 1 dog in each group prior to limb amputation. Pamidronate disodium and palliative radiation therapy were also provided to 1 dog in the carboplatin group after it developed bone metastasis following carboplatin chemotherapy. Toceranib phosphate (2.5 mg/kg [1.1 mg/lb], PO, 3 d/wk) was administered to 4 dogs (2/group) after they developed pulmonary metastasis. Four dogs in the carboplatin-MC group received metronomic chlorambucil chemotherapy (4 mg/m², PO, q 24 h) as an alternative to MC treatment after they developed cystitis.

**Histologic subtype and grade**

Histologic slides of osteosarcoma specimens from 34 (87%) dogs were available for reevaluation, but tumor grade could not be assessed for 1 dog because of artifact. The diagnosis of osteosarcoma was confirmed for all 34 dogs. No significant differences in distributions of tumors by grade or subtype were identified between the 2 groups (Table 1).

**Outcome**

Four (20%) dogs in the carboplatin group and 6 (32%) dogs in the carboplatin-MC group survived to the time of analysis. One dog in the carboplatin group was lost to follow-up 315 days after limb amputation. The remaining 28 (72%) dogs were euthanized owing to progressive disease. Median follow-up period for the 11 (28%) dogs that survived and were censored from the OST analysis was 450 days (range, 204 to 1,400 days). Median follow-up period for dogs in the carboplatin-MC group was 464 days and for dogs in the carboplatin group was 348 days.

Median PFT for all dogs was 402 days (95% CI, 285 to 519 days), and median OST was 464 days (95% CI,
Figure 1—Kaplan-Meier curves of PFT following limb amputation for dogs with a histologic diagnosis of appendicular osteosarcoma that underwent limb amputation and completed carboplatin chemotherapy followed with \( n = 19 \) (solid line) or without \( (n = 20 \) dashed line) MC chemotherapy (15 mg/m\(^2\), PO, q 24 h) and meloxicam (0.1 mg/kg [0.045 mg/lb], PO, q 24 h). Median PFT was 480 days for dogs that received carboplatin and MC chemotherapy and 244 days for dogs that received only carboplatin chemotherapy \((P = 0.14)\). Hatch marks indicate censored dogs.

Figure 2—Kaplan-Meier curves of OST for dogs in Figure 1. Median OST for dogs that received carboplatin and MC chemotherapy was 480 days and for dogs that received carboplatin chemotherapy alone was 458 days \((P = 0.24)\). See Figure 1 for remainder of key.
to 492 days). Dogs in the carboplatin-MC group had a longer median PFT (480 days; 95% CI, 264 to 696 days) than dogs in the carboplatin group (244 days; 95% CI, 0 to 509 days), but this difference was not significant (P = 0.14; Figure 1). Similarly, dogs in the carboplatin-MC group had a longer median OST (480 days) than dogs in the carboplatin group (458 days), but again this difference was not significant (P = 0.24; Figure 2).

**Discussion**

In the present study, the effectiveness of maintenance MC chemotherapy following limb amputation and carboplatin chemotherapy was retrospectively investigated in dogs with appendicular osteosarcoma. Following amputation, dogs that received adjuvant carboplatin chemotherapy followed by MC chemotherapy had a longer median PFT (approx 16 months) than dogs treated with carboplatin only (approx 8 months), but this difference was not significant. This finding suggested that daily adjuvant maintenance with MC chemotherapy at 15 mg/m²/d, PO, with concurrent NSAID administration may not be effective in dogs with osteosarcoma.

Previous studies revealed a similar survival time for dogs with appendicular osteosarcoma treated with limb amputation and MTD plus MC chemotherapy as for dogs treated with limb amputation and MTD chemotherapy alone in other reports, and reported median PFTs range from 6 to 8 months. The lack of a difference in median PFT between groups in the present study might have been attributable to low statistical power. To detect a PFT difference of 8 months in the study dogs, with an α value of 0.05 and a β value of 0.20, 107 dogs would have been required in total, and for OST, this number would have been 103. Ideally, prospective randomized studies with appropriate sample sizes would be conducted to determine whether no difference truly exists between treatment protocols.

One of the most notable findings of the study reported here was the high prevalence of cystitis in dogs that received MC chemotherapy. Median duration of MC chemotherapy was 3 months, whereas this treatment was discontinued for 58% of dogs because they developed cystitis, and only 6 of 18 dogs received MC chemotherapy for > 4 months (data not shown). The brief treatment duration could explain why no associated survival benefit was observed. Cyclophosphamide is metabolized in the liver, then eventually converted to acrolein, which irritates the mucosa of the urinary bladder and can induce sterile hemorrhagic cystitis. To prevent the development of sterile hemorrhagic cystitis in dogs receiving MTD cyclophosphamide chemotherapy, prophylactic furosemide or mesna administration could be considered.

In addition, regular performance of routine urinalyses could allow early detection of microscopic hematuria and subsequent discontinuation of cyclophosphamide administration to avoid development of severe signs of sterile hemorrhagic cystitis.

Median PFT and OST in the study reported here were relatively long, compared with data in previous studies, likely owing to case selection bias. Dogs with evidence of progressive disease prior to receiving the final dose in the carboplatin protocol were excluded from the study, resulting in potential selection of dogs with less biologically aggressive osteosarcoma. Because dogs were required to have completed the carboplatin protocol to be included, they also consequently needed to have survived for at least 14 to 20 weeks after limb amputation. The observed OSTs were consistent with the survival time reported for dogs with osteosarcoma that completed an MTD chemotherapy protocol. However, the survival times in the present study should be considered carefully given the low prevalence of high serum ALP activity (2/37 [5%]) and advanced age (only 4 [11%] dogs < 5 years of age) of included dogs, both of which are factors associated with prognosis in dogs with appendicular osteosarcoma.

The prescribed number of doses ranged from 4 to 6 in the carboplatin chemotherapy protocol over the 5-year study period at the Ontario Veterinary College. A prospective study involving 4 doses of adjuvant carboplatin chemotherapy for dogs with osteosarcoma yielded a median OST of 321 days. In a different study involving 470 dogs with osteosarcoma, multivariable analysis controlling for other factors revealed no difference in PFT or OST between 4 and 6 doses of adjuvant carboplatin chemotherapy. In the present study, there was no difference between groups in the median number of carboplatin doses.

An important limitation of the present study was its retrospective nature and small sample size. A lack of availability of complete medical records could have veiled potentially important findings. Data regarding toxic effects also could have been underestimated because of the limited available information. The small sample size also could have contributed to type II error.

Overall, findings of the present study suggested that MC chemotherapy (with concurrent meloxicam administration) following limb amputation and carboplatin chemotherapy may not improve survival time in dogs with appendicular osteosarcoma. Because more than half of the dogs discontinued MC treatment because of cystitis, prophylactic treatment for the cystitis such as furosemide or mesna could be considered for dogs enrolled in future randomized controlled clinical trials of MC chemotherapy to avoid this strong possibility. Given that the immunomodulatory effects of MC chemotherapy were
not assessed in the present study, specific immunologic alterations, such as changes in regulatory T-cell counts or circulating cytokine concentrations, need to be investigated prospectively in comparison with clinical outcomes.

Footnotes
a. Hospira Inc. Lake Forest, Ill.
b. Boehringer Ingelheim, Ingelheim am Rhein, Germany.
c. Chiron Compounding Pharmacy Inc, Guelph, ON, Canada.
d. SPSS, version 23.0, SPSS Inc, Chicago, Ill.

References