Evaluation of Weight Change During Carboplatin Therapy in Dogs With Appendicular Osteosarcoma

A.L. Story [iD], S.E. Boston, J.J. Kilkenny, A. Singh, J.P. Woods, W.T.N. Culp, K.A. Skorupski, and X. Lu

Background: The prevalence of cancer cachexia in veterinary medicine has not been studied widely, and as of yet, no definitive diagnostic criteria effectively assess this syndrome in veterinary patients.

Objectives: (1) To determine the patterns of weight change in dogs with appendicular osteosarcoma treated with amputation and single-agent carboplatin during the course of adjuvant chemotherapy; and (2) to determine whether postoperative weight change is a negative prognostic indicator for survival time in dogs with osteosarcoma.

Animals: Eighty-eight dogs diagnosed with appendicular osteosarcoma. Animals were accrued from 3 veterinary teaching hospitals.

Methods: Retrospective, multi-institutional study. Dogs diagnosed with appendicular osteosarcoma and treated with limb amputation followed by a minimum of 4 doses of single-agent carboplatin were included. Data analyzed in each patient included signalment, tumor site, preoperative serum alkaline phosphatase activity (ALP), and body weight (kg) at each carboplatin treatment.

Results: A slight increase in weight occurred over the course of chemotherapy, but this change was not statistically significant. Weight change did not have a significant effect on survival. Institution, patient sex, and serum ALP activity did not have a significant effect on survival.

Conclusions and Clinical Importance: Weight change was not a prognostic factor in these dogs, and weight loss alone may not be a suitable method of determining cancer cachexia in dogs with appendicular osteosarcoma.

Key words: Cachexia; Canine; Chemotherapy; Oncology.

Cancer cachexia is a complex syndrome that affects human and veterinary patients. In the human medical literature, cancer cachexia has been defined by international consensus as a loss of skeletal muscle mass with or without a loss of fat mass and develops as a consequence of decreased caloric intake and abnormal metabolism.[1] Cancer cachexia is associated with decreased survival and quality of life in human patients with advanced cancer.[2,3] The prevalence of this syndrome in veterinary medicine has not been widely studied, and as of yet, no definitive diagnostic criteria effectively assess cancer cachexia in veterinary patients.

Abbreviations:

ALP	alkaline phosphatase
BCS	body condition score
CT	computed tomography

One study investigated cancer cachexia characterized by body condition score (BCS) in 100 dogs at the time of presentation to a veterinary oncology service.[4] In that study, 4% of the dogs had cachexia, defined as a BCS ≤3 of 9 and 15% percent had moderate-to-severe muscle wasting.[4] The investigators concluded that BCS alone may not be sensitive enough to detect cancer cachexia. A similar study of 57 cats that were treated for various neoplastic conditions reported that feline cancer patients with BCS <5 had significantly shorter median survival time compared to cats with BCS ≥5.[5] Similarly, that study also showed a significant association between body weight and median survival time.[5]

A recent study of dogs assessed the effect of obesity on survival time in dogs with lymphoma and osteosarcoma.[6] The study did not find that BCS was associated with survival time in dogs with osteosarcoma, but did find that underweight dogs with lymphoma had a significantly shorter survival time than dogs that maintained or gained weight.[6]

Weight loss has been shown to be a negative prognostic indicator for response to chemotherapy, surgical risk and survival time in human cancer patients.[3,7] A retrospective study assessing weight change during chemotherapy in women with ovarian cancer found that increasing body weight during therapy was associated with improved overall survival, whereas weight loss was associated with poor overall survival.[8]

Appendicular osteosarcoma is a relatively common and aggressive cancer in dogs, accounting for up to 85% of all canine primary bone tumors.[9,10] Amputation and chemotherapy are the standard of care for osteosarcoma, with single-agent carboplatin being a commonly used protocol for this disease.[11–17] We have noted anecdotally that some canine osteosarcoma patients experience substantial weight loss over the course of postamputation chemotherapy. However, it is not known how commonly this occurs, or its potential effect on prognosis.

The objectives of our study were as follows: (1) to determine the patterns of weight change in dogs with appendicular osteosarcoma treated with amputation and single-agent carboplatin during the course of adjuvant chemotherapy; (2) and determine whether postoperative weight change is a negative prognostic indicator for survival time in dogs with osteosarcoma. We hypothesized that canine osteosarcoma patients would lose weight during the course of carboplatin chemotherapy and that patients with weight loss would have decreased survival time compared to those with static or increased weight during treatment.

Materials and Methods

Ours was a retrospective multi-institutional study. Cases were accrued from the University of Florida, College of Veterinary Medicine, the University of California-Davis, School of Veterinary Medicine, and the University of Guelph, Ontario Veterinary College. Inclusion criteria were dogs with histologically confirmed osteosarcoma that were treated with limb amputation followed with intent-to-treat of 6 doses of carboplatin, with a minimum of 4 doses administered. Exclusion criteria were patients that underwent a limb-sparing procedure, received chemotherapy before amputation, or were treated with combination chemotherapy protocols during carboplatin treatment. Dogs that received additional chemotherapeutic agents and bisphosphonates after completing their carboplatin protocol were included. Data collected from each patient included signalment, tumor site, preoperative serum alkaline phosphatase activity (ALP), cytology results if available, preoperative diagnostic imaging results (eg, chest radiographs, bone scan, thoracic computed tomography [CT], whole body CT), presence or absence of gross metastasis, number of doses of carboplatin administered, additional therapies administered, date and location of metastasis, date of last follow-up, and date and cause of death. Weight (kg) before amputation and at each chemotherapy administration was recorded. Patient age was defined as age (days) at the date of amputation. Survival time was defined as the date of amputation to the date of death (days). Weight at the time of the first administration of carboplatin was used as baseline weight. Weight loss was defined as any weight lower than baseline.

Statistical Analysis

Descriptive statistics (median [range]) for continuous variables; number [N] and proportion for categorical variables) were used for summarizing the data. Weight change for each dog was computed as the difference in weight between the last and first carboplatin dose that the dog received. Overall survival time, defined as the time from the date of amputation to the date of death or last follow-up, was compared between groups by the Log-rank test. The corresponding hazard ratio and its 95% confidence interval were estimated through the Cox proportional hazard regression model.

Results

Eighty-eight dogs met the inclusion criteria. There were 45 castrated males, 5 intact males, 36 spayed females, and 2 intact females. The most common breeds represented were Golden Retrievers (13%), Rottweilers (13%), Labrador Retrievers (11%), Doberman Pinschers (8%), mixed breed (8%), Greyhounds (7%), Mastiffs (7%), and Great Danes (6%). All other breeds represented <4% of study dogs. Pre-amputation body weight ranged from 21 to 94 kg with a median body weight of 39.7 kg. The most frequent tumor sites were distal radius (N = 28), proximal humerus (N = 20), distal femur (N = 14), proximal tibia (N = 9), and distal tibia (N = 9). All other sites consisted of ≤4 cases per site. Thirty-seven dogs received 4 doses of carboplatin, 16 received 5 doses, and 35 received 6 doses. Of 80 dogs with preoperative ALP activity available, 11 had increased activity. The overall median survival time for the dogs was 360 days (range, 289–461). Institution (P = .7626), patient sex (P = .3283), age (P = .1788), body weight at dose 1 (P = .1334), number of doses of carboplatin (P = .1593), and ALP activity (P = .5991) did not have a significant effect on survival.

Of the 88 dogs in our study, 36 lost weight during treatment, 3 had stable weight, and 49 gained weight. The mean percentage weight changes from dose 1–4, 1–5, and 1–6 were 1.5, 2.2, and 0.3%, respectively, indicating a slight increase in weight (Fig 1). Overall, weight did not vary significantly during the course of carboplatin treatment. Weight change did not have a significant effect on survival (P = .1044).

Discussion

Signalment, body weight, tumor site, and median survival time were consistent with previous reports of dogs with appendicular osteosarcoma.[9,11–14,16,18] Of the dogs
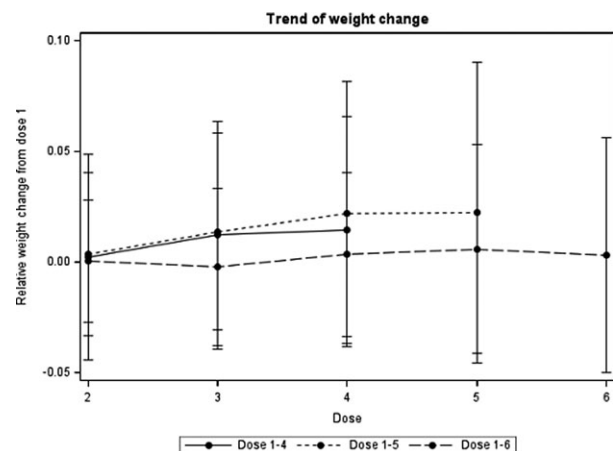

Fig 1. Weight change (%) at carboplatin doses 4, 5, and 6, relative to dose 1. Weight change (%) was evaluated between doses 4, 5, and 6 of carboplatin relative to dose 1. The solid line represents dose 4 relative to dose 1 (37 dogs), the small dashed line represents dose 5 relative to dose 1 (16 dogs), and the large dashed line represents dose 6 relative to dose 1 (35 dogs).

with available preoperative ALP activity, 14% had increased activity, and increased ALP activity did not have a significant prognostic effect. This result differs from previous studies, in which increased ALP activity was a negative prognostic factor.[18,19] This finding may be due to type II error because of the low number of dogs in our study with increased ALP activity.

Our first aim was to characterize the weight change that occurred during standard of care treatment of osteosarcoma in dogs. Although weight change was not a significant prognostic indicator of survival, we did notice an overall slight increase in body weight in 56% of dogs during treatment. However, this change was not statistically significant, indicating that, for this population of dogs, weight generally was stable or increased slightly during chemotherapy. This finding may be attributable to decreased physical activity after amputation, lack of client instruction to decrease caloric intake with decreased activity or both. The slight weight gain also may have been a consequence of owners giving their dogs more food to treat them due to the fact that they had cancer. These data caused us to reject our first hypothesis that dogs would lose weight during the course of therapy.

We did not have enough dogs that experienced weight loss in our study to assess whether or not weight loss was a negative prognostic indicator. Therefore, we rejected our second hypothesis that weight loss would be a negative prognostic indicator for survival for affected dogs. In fact, overall, weight loss was not a characteristic of this population of dogs. Cancer cachexia may be uncommon in dogs with osteosarcoma, and a study of a larger group of affected dogs would be necessary to determine whether weight loss is a factor in prognosis. Weight loss alone also may be an insensitive variable to assess cancer cachexia. Limitations of our study included lack of available body and muscle condition scores, appetite history, and diet history.

Loss of lean body mass is the defining characteristic of cachexia, and therefore, other factors such body condition in conjunction with muscle condition also should be taken into account.[1,20] Body condition scoring assesses adipose tissue, and at normal and overweight body conditions, it can be difficult to evaluate muscle wasting.[21–23] For this reason, we recommend that future studies use consistent methods and scales of assessing body condition as well as muscle condition to more appropriately assess cachexia.[21–24]

More recent studies in veterinary and human medicine have aimed to assess lean body mass using dual energy X-ray absorptiometry and CT and ultrasound measurements of epaxial musculature.[1,25,26] Dual energy X-ray absorptiometry is used to assess body composition, and CT and ultrasound measurements compare cross-sectional or transverse views, respectively, of the epaxial musculature in dogs. In 1 study, epaxial muscle area was significantly lower in older, sarcopenic animals compared to younger animals.[26] Additional studies are needed to assess the accuracy and limitations of these methods in animals.

In conclusion, dogs with appendicular osteosarcoma in our study treated with amputation and adjunctive carboplatin therapy did not experience significant weight loss and actually experienced slight weight gain during treatment. Weight change was not prognostic in this group of dogs, and weight loss alone may not be a suitable method of determining cancer cachexia in dogs with appendicular osteosarcoma. Additional studies assessing weight change, BCS, and muscle mass, as well as incorporation of physiotherapy and nutritional management of veterinary patients, are needed to assess the effects of nutrition and changes in metabolism associated with cancer on prognosis.

References

1. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12:489–495.
2. Fearon K, Barber M, Moses A. The cancer cachexia syndrome. Surg Oncol Clin N Am 2001;10:109–126.
3. DeWys WD, Begg C, Lavin PT, et al. Prognostic effect of weight loss prior to chemotherapy in cancer patients. Am J Med 1980;69:491–497.
4. Michel KE, Sorenmo K, Shofer FS. Evaluation of body condition and weight loss in dogs presented to a veterinary oncology service. J Vet Intern Med 2004;18:692–695.
5. Baez JL, Michel KE, Sorenmo K, et al. A prospective investigation of the prevalence and prognostic significance of weight loss and changes in body condition in feline cancer patients. J Feline Med Surg 2007;9:411–417.
6. Romano FR, Heinze CR, Barber LG, et al. Association between body condition score and cancer prognosis in dogs with lymphoma and osteosarcoma. J Vet Intern Med 2016;30:1179–1186. https://doi.org/10.1111/jvim.13965.
7. Daly JM, Dudrick SJ, Copeland EM. Evaluation of nutritional indices as prognostic indicators in the cancer patient. Cancer 1979;43:925–931.
8. Hess LM, Barakat R, Tian C, et al. Weight change during chemotherapy as a potential prognostic factor for stage III epithelial ovarian carcinoma: A Gynecologic Oncology Group study. Gynecol Oncol 2007;107:260–265.
9. Brodey RS, Riser WH. Canine osteosarcoma. A clinicopathologic study of 194 cases. Clin Orthop 1969;62:54–64.
10. Dorfman SK, Hurvitz AI, Patnaik AK. Primary and secondary bone tumours in the dog. J Small Anim Pract 1977;18:313–326.
11. Spodnick GJ, Berg J, Rand WM, et al. Prognosis for dogs with appendicular osteosarcoma treated by amputation alone: 162 cases (1978–1988). J Am Vet Med Assoc 1992;200:995–999.
12. Straw RC, Withrow SJ, Richter SL, et al. Amputation and cisplatin for treatment of canine osteosarcoma. J Vet Intern Med 1991;5:205–210.
13. Mauldin GN, Matus RE, Withrow SJ, et al. Canine osteosarcoma. Treatment by amputation versus amputation and adjuvant chemotherapy using doxorubicin and cisplatin. J Vet Intern Med 1988;2:177–180.

14. Thompson JP, Fugent MJ. Evaluation of survival times after limb amputation, with and without subsequent administration of cisplatin, for treatment of appendicular osteosarcoma in dogs: 30 cases (1979–1990). J Am Vet Med Assoc 1992;200:531–533.

15. Kraegel SA, Madewell BR, Simonson E, et al. Osteogenic sarcoma and cisplatin chemotherapy in dogs: 16 cases (1986–1989). J Am Vet Med Assoc 1991;199:1057–1059.

16. Bergman PJ, MacEwen EG, Kurzman ID, et al. Amputation and carboplatin for treatment of dogs with osteosarcoma: 48 cases (1991 to 1993). J Vet Intern Med 1996;10:76–81.

17. Dernell WS, Straw RC, Withrow SJ. Tumors of the skeletal system. In: Withrow SJ, MacEwen EG, eds. Small Animal Clinical Oncology. Philadelphia, PA: WB Saunders; 2001:378–417.

18. Ehrhart N, Dernell WS, Hoffman WE, et al. Prognostic importance of alkaline phosphatase activity in serum from dogs with appendicular osteosarcoma: 75 cases (1990–1996). J Am Vet Med Assoc 1998;213:1002–1006.

19. Garzotto CK, Berg J, Hoffman WE, et al. Prognostic significance of serum alkaline phosphatase activity in canine appendicular osteosarcoma. J Vet Intern Med 2000;14:587–592.

20. Freeman LM. Cachexia and sarcopenia: Emerging syndromes of importance in dogs and cats. J Vet Intern Med 2012;26:3–17.

21. Laflamme DP. Development and validation of a body condition score system for dogs. Canine Pract 1997;22:10–15.

22. Michel KE, Anderson W, Cupp C, Laflamme D. Correlation of a feline muscle mass score with body composition determined by DEXA. Br J Nutr 2011;106(Suppl 1):S57–S59.

23. WSAVA Nutritional Assessment Guidelines Task Force Members. Nutritional assessment guidelines. J Small Anim Pract 2011;52:385–396.

24. Michel KE, Anderson W, Cupp C, et al. Validation of a subjective muscle mass scoring system for cats. J Anim Physiol Anim Nutr 2009;93:806.

25. Lawler DF, Larson BT, Ballam JM, et al. Diet restriction and ageing in the dog: Major observations over two decades. Br J Nutr 2009;99:793–805.

26. Hutchinson D, Sutherland-Smith J, Watson AL, et al. Assessment of methods of evaluating sarcopenia in old dogs. Am J Vet Res 2012;73:1794–1800.