Use of carboplatin for treatment of dogs with malignant melanoma: 27 cases (1989–2000)

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Objective—To evaluate response rate and duration of malignant melanomas in dogs treated with carboplatin.

Design—Retrospective study.

Animals—27 client-owned dogs with spontaneously occurring measurable malignant melanomas.

Procedure—Records of dogs with melanomas treated with carboplatin from October 1989 to June 2000 were reviewed. Carboplatin was administered IV at doses of 300 or 350 mg/m^2 of body surface area. Response to treatment and evidence of drug toxicity were determined.

Result—Response to treatment could be evaluated in 25 dogs. Of those, overall response rate was 28%. One dog had a complete response, 6 (24%) dogs had a partial response (> 50% reduction in tumor burden). Median duration of partial response was 165 days. Eighteen dogs had stable disease (n = 9; 36%) or progressive disease (9; 36%). Response to treatment was significantly associated with carboplatin dose on a milligram per kilogram basis (15.1 mg/kg [6.9 mg/lb] of body weight vs 12.6 mg/kg [5.7 mg/lb]). Evidence of gastrointestinal toxicosis could be assessed in 27 dogs. Mean body weight of 5 dogs that developed gastrointestinal toxicosis was significantly less than that of 22 dogs without gastrointestinal toxicosis (9.9 kg [21.8 lb] vs 19.3 kg [42.5 lb]).

Conclusions and Clinical Relevance—Carboplatin had activity against macroscopic spontaneously occurring malignant melanomas in dogs and should be considered as an adjunctive treatment for microscopic local or metastatic tumors. Gastrointestinal toxicosis was associated with body weight. Because small dogs are more likely to have adverse gastrointestinal effects, gastrointestinal protectants should be considered for these patients. (*J Am Vet Med Assoc* 2001;218:1444–1448)

Melanomas are common tumors of the skin, eye, and oropharynx in dogs. Most dermal and ocular melanomas are benign and recurrence or metastasis after adequate excision or enucleation is rare.[1-5] In contrast, melanomas of the oral cavity, digits, and mucocutaneous junctions in dogs are associated with a poor prognosis because of rapid invasion of surrounding normal tissue and high likelihood of regional and distant metastasis early in the course of the disease.[1,2,6-13]

Carboplatin (*cis*-diammine [1,1-cyclobutanedicarboxylato] platinum [II]), an analogue of cisplatin, is a widely used chemotherapeutic agent with demonstrated activity against numerous solid tumors in humans.[14] In patients with advanced malignant melanoma, phase-II clinical trials of carboplatin have response rates from 11 to 19%.[15-17] In a canine melanoma cell line, carboplatin had marked in vitro cytotoxicity in short-term growth assays.[18] Clinical reports describing the use of carboplatin in spontaneous tumors in animals are limited.[19-22] The objective of the study reported here was to evaluate the efficacy of carboplatin in dogs with measurable melanomas.

Criteria for Selection of Cases

Medical records of 40 dogs with melanomas treated with carboplatin from October 1989 to June 2000 were reviewed. Criteria for inclusion were histologically confirmed diagnosis of malignant melanoma, measurable tumors, carboplatin treatment, and no concurrent treatment for melanoma.

Procedures

All dogs underwent clinical evaluation that included a baseline CBC, serum biochemical profile, and 3 radiographic views of the thorax. Fine-needle aspiration of regional lymph nodes for cytologic evaluation was performed when possible. When applicable, radiographs of the primary tumor were also obtained to assess bone involvement. Tumors were either directly measured with calipers or imaged and measured by radiographic methods. Tumor volume was estimated by measuring masses in 3 dimensions, and when affected lymph nodes were present, volumes were added to calculate the total tumor volume. Oral melanomas were staged according to World Health Organization Tumor, Nodule, Metastasis guidelines.[23] Age, breed, sex, and history of previous treatment (eg, surgery, chemotherapy, or radiation therapy) were recorded for each dog.

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Treatment protocol—Carboplatin[a] was administered IV at doses of 300 mg/m^2 (dogs < 15 kg [33 lb]) or 350 mg/m^2 (dogs ≥ 15 kg) of **body surface area (BSA)**. Body surface area was calculated by use of the equation: $(10.1 \times [\text{body weight (g)}^{0.67}])/10^4$. Treatment was repeated every 21 days until no further response was observed. A CBC was performed 7, 14, and 21 days after the first treatment. If either neutropenia (< 1,000 cells/µl) or fever (rectal temperature, > 39.4 C [103 F]) was observed, orally administered antimicrobials (trimethoprim-sulfadiazine, 15 mg/kg [6.8 mg/lb] of body weight, PO, q 12 h) were prescribed, and the dose of carboplatin was reduced by 25% for the duration of treatment.

Evaluation of response and toxicosis—Dogs were evaluated by use of physical examination 7, 14, and 21 days after treatment with carboplatin. Tumor response was determined by measuring the tumors, as described. Response to treatment was categorized as follows: **complete response (CR)**, 100% reduction in size of all measurable tumors; **partial response (PR)**, > 50 to < 100% reduction; **stable disease (SD)**, < 50% reduction or no change in size of all measurable tumors and lack of appearance of new tumors; and **progressive disease (PD)**, increase of > 25% in size of all measurable tumors or the appearance of new tumors. For all categories, response was required to last ≥ 21 days. Decreases in tumor size for shorter durations were defined as SD.

Evidence of drug toxicity was monitored by evaluation of laboratory data, physical examination, and historical facts obtained from owners. Gastrointestinal toxicoses were graded according to modified criteria (**Appendix**).

Statistical analyses—Duration of disease was defined as the interval between first diagnosis of malignant melanoma and first treatment with carboplatin. Duration of response was calculated in days from the time of maximal response until recurrence of disease for dogs that achieved a CR or until PD for dogs that achieved PR. Carboplatin dose was calculated as milligrams per kilogram of body weight. The Mann-Whitney *U* test was used to compare responders and nonresponders with respect to age, weight, tumor size, carboplatin dose (milligrams per kilogram), and duration of disease before treatment with carboplatin and to evaluate associations between gastrointestinal toxicosis and body weight or carboplatin dose (milligrams per kilogram). Responders and nonresponders were compared by use of a Pearson χ^2 test with respect to previous response to radiation treatment, sex, carboplatin dose (milligrams per square meter of BSA), stage, whether the tumor was a primary or metastatic lesion, and development of gastrointestinal toxicosis. All variables were analyzed singly in a univariate model. Significant variables ($P \leq 0.05$) defined in the univariate model were analyzed by use of multivariate linear regression. All statistical analyses were performed with computer software.[b]

Results

Dogs—Twenty-seven dogs met the inclusion criteria. Median and mean age of the 27 dogs was 11 years (range, 1 to 19 years). Seventeen dogs were male, and 10 were female. Eighty-five percent (23/27) of dogs were purebred dogs, and 15% (4/27) were mixed-breed dogs. Of the purebred dogs, 5 were Poodles, and 5 were Miniature Schnauzers. Median and mean body weights were 13.2 and 17.6 kg (29 and 38.7 lb), respectively (range, 3.6 to 54.8 kg [7.9 to 120.6 lb]). Median and mean durations of disease before treatment with carboplatin were 98 and 283 days, respectively (range, 0 to 2,201 days).

All dogs had measurable tumors at the time of treatment with carboplatin. Tumor volume was not calculated for 7 dogs with radiographic evidence of pulmonary metastases. For the remaining 20 dogs, tumor volume ranged from 0.4 to 81 cm^3, with median and mean volumes of 5.2 and 13.3 cm^3, respectively. Twenty-five dogs had melanomas of the oral cavity, 1 had a melanoma of the dermis of the metatarsus, and 1 had a recurrent melanoma in the dermis of the inguinal region. Twelve of the 27 (44%) dogs had metastases to regional lymph nodes, and 7 (26%) had pulmonary metastases. Of the 25 dogs with oral tumors, 2 (8%) had stage-I tumors, 3 (12%) had stage-II tumors, 13 (52%) had stage-III tumors, and 7 (28%) had stage-IV tumors.

Thirteen dogs with oral melanomas were treated by use of surgery before receiving carboplatin. Median and mean disease-free intervals after excision were 57 and 299 days, respectively (range, 15 to 2,180 days). Twelve dogs had local recurrence, and 1 dog developed pulmonary metastases after surgery but no local recurrence. Of the dogs with local recurrence, 3 had metastases to the regional lymph node, 1 had pulmonary metastases, and 1 had lymph node and pulmonary metastases. Seven of the 27 dogs received radiation treatment prior to administration of carboplatin. Dogs received 30 Gy orthovoltage radiation in 3 equal fractions delivered on days 0, 7, and 21. Overall median progression-free interval was 66 days (mean, 166 days). Four dogs had local recurrence, and 3 dogs had metastases after radiation treatment. Measurable response to radiation treatment could be evaluated in 4 of the 7 dogs (3 dogs received radiation treatment adjunctive to microscopically incomplete excision). Two dogs had a CR to radiation treatment for 61 and 209 days, respectively, and 2 dogs had a PR for 50 and 54 days, respectively. All dogs had recurrent tumors at the time they received carboplatin.

Treatments and toxicosis—Eighty-nine treatments with carboplatin were administered to the 27 dogs; median number of treatments was 2 (mean, 3; range 1 to 18). For each dog, the number of treatments administered was 1 (n = 10), 2 (10), 3 (1), 5 (1), 6 (1), 7 (1), 9 (1), 11 (1), or 18 (1). Sixteen dogs received a dose of 300 mg/m^2, and 11 dogs received 350 mg/m^2. After the first treatment, the dose of carboplatin was reduced by 25% in 2 dogs that received 300 mg/m^2 because of neutropenia and fever in 1 dog and severe adverse gastrointestinal effects in the other.

Gastrointestinal toxicosis developed in 5 dogs after treatment with carboplatin. Among dogs that received a dose of 300 mg/m^2, 4 dogs had signs as follows: 4 had anorexia (grade 1 [n = 1]; grade 2 [3]), 4

had vomiting (grade 2 [2], grade 3 [1], grade 4 [1]), and 3 had diarrhea (grade 3 [1]; grade 4 [2]). Among dogs that received a dose of 350 mg/m^2, 1 dog had vomiting (grade 2). Adverse effects developed after the first treatment in 3 dogs and after the first and second treatments in 2 dogs. One dog was euthanatized because of severe gastroenteritis; weight of this dog was 3.6 kg (7.9 lb). Body weight was significantly associated with gastrointestinal toxicosis; mean body weight of the 5 dogs that developed gastrointestinal toxicosis was significantly (P = 0.036) less than that of the other 22 dogs (9.9 kg [21.8 lb] vs 19.3 kg [42.5 lb]). Dogs that developed gastrointestinal toxicosis received a mean dose of 15.7 mg of carboplatin/kg at each treatment, compared with a dose of 13.0 mg/kg for dogs without gastrointestinal toxicosis; however, the difference between these groups was not significant (P = 0.094).

Response to treatment—Response to carboplatin could be evaluated in 25 dogs. Two dogs that received 300 mg/m^2 were euthanatized 5 and 14 days after carboplatin treatment because of severe gastroenteritis and sepsis, respectively. The overall response rate was 28% (7/25). One dog, an 11-year-old Scottish Terrier with a melanoma of the caudal portion of the mandible and lymph node metastases, had a CR to 9 treatments with carboplatin. The dog was in complete remission when it was euthanatized 950 days after initiation of treatment. Six of the 25 (24%) dogs had a PR to carboplatin for a median duration of 165 days (mean, 163 days; range, 42 to 266 days). Treatment with carboplatin resulted in SD in 9 of the 25 (36%) dogs. Duration of SD could not be determined, because treatment was not continued for all dogs. The remaining 9 (36%) dogs had PD.

Of the 14 dogs that received a dose of 300 mg/m^2 and were able to be evaluated for response, 1 had CR, 5 had PR, and the remaining 8 had SD or PD. Of the 11 dogs that received 350 mg/m^2, 1 had PR, and the remaining 10 had SD or PD. There was no significant difference between carboplatin dose (mg/m^2) and response.

In the univariate model, body weight and carboplatin dose (mg/kg) were significantly associated with response. Mean body weight of 7 responders was significantly (P = 0.006) lower than that of 18 nonresponders (9.4 kg [20.7 lb] vs 21.8 kg [48 lb]). Mean dose of carboplatin administered at each treatment to dogs that responded was 15.1 mg/kg, compared with 12.6 mg/kg given to dogs that did not respond (P = 0.007). After multivariate analysis, only carboplatin dose (mg/kg) retained significance (P = 0.002). There were no significant differences between responders and nonresponders with respect to age, sex, tumor size, or duration of disease before receiving carboplatin. Similarly, there were no significant differences between responders and nonresponders for response to radiation treatment, tumor stage, or whether the tumor was a primary or metastatic lesion.

Discussion

Carboplatin is a second generation platinum compound. In the retrospective study reported here, carboplatin caused a measurable response in 28% (7/25) of dogs with malignant melanomas. Most dogs were entered into the study after having melanoma for a substantial duration (median, 98 days), because many had been treated by use of multiple resections or radiation prior to carboplatin treatment. Also, many of the dogs had large tumor burdens and advanced tumor stages. Although there was no significant association between response and duration of tumors prior to receiving carboplatin, tumor size, or tumor stage, these factors may all affect evaluation of a drug. Our results suggest that carboplatin is useful for dogs with macroscopic tumors and in addition, may be useful as an adjunctive treatment for microscopic local tumors, systemic tumors, or both.

Local and systemic tumor control is the fundamental goal in the management of dogs with malignant melanomas. In 1 study,[6] median survival of dogs with untreated oral melanomas was 65 days. Aggressive resection by mandibulectomy or maxillectomy can be effective in control of oral tumors; however, postsurgical recurrence develops in 8 to 85% of dogs, and metastasis to regional lymph nodes, lungs, or other viscera may develop in as many as 95%.[1,24-27] Mean survival time for dogs treated by use of excision is approximately 8 months.[6,24-26,28]

Radiation treatment effectively achieves local control in dogs with melanomas. Reduction in tumor size is attained in 83 to 94% of dogs, and as many as 70% have a CR.[29,30] However, the prognosis is still poor, because metastasis develops early in the course of disease. In 1 study,[29] 21 of 36 (58%) dogs died of metastatic tumors.

Other forms of local treatment have been reported,[31] but because disseminated tumors are common, effective systemic treatment is essential. Measurable responses have been observed in dogs after various systemic treatments. Regression of growth of a gingival malignant melanoma in a dog developed after repeated injections of mixed bacterial toxin.[32] Objective responses were also seen in dogs treated with tumor necrosis factor and interleukin-2.[27] More recently, autologous tumor vaccines made from irradiated tumor cells transfected with human granulocyte-macrophage colony-stimulating factor have been used, resulting in responses in 2 of 10 dogs.[33]

Investigation into immunotherapy and biological response modification for dogs with malignant melanomas is continuing. In a recent study,[34] dogs with oral melanomas were treated with surgery followed by **liposome-encapsulated muramyl tripeptide-phosphatidylethanolamine (L-MTP-PE)**, which is an activator of monocyte and macrophage tumoricidal activity. Results of that study suggested that L-MTP-PE administered after surgery prolonged survival time in dogs with early-stage (stage I) oral melanoma.

Few controlled studies have evaluated the use of chemotherapeutic agents for dogs with malignant melanomas. Melphalan appears to be an active agent when administered IV. In 1 study, 3 of 11 dogs had measurable responses, with a 4-month median time to progression.[35] Treatments with other drugs have been attempted, but few reports of these have been made.[13,36-39]

Small dogs with malignant melanomas appeared to be more likely to respond to carboplatin treatment than large dogs. Results of studies of dogs with lymphoma and osteosarcoma indicate that body weight is of prognostic importance, because small dogs have increased durations of remission and survival.[19,40-42] Results of in vitro studies indicate that tumor cell survival depends on drug concentration and exposure time to the drug.[43] When BSA rather than body weight is used to calculate doses, small dogs receive more drug per kilogram than do large dogs. Results of multivariate analysis in the study reported here indicated this as the reason that more measurable responses were detected in small dogs.

Small dogs also appeared to be more likely to develop gastrointestinal toxicosis after carboplatin treatment. Clinical toxicosis in small versus large dogs treated with various chemotherapy agents has been reported in other studies.[44-47] Increased incidence of adverse effects in small dogs may result because most drugs are calculated on the basis of estimated BSA, and small dogs therefore receive more drug per kilogram of body weight. Body surface area is used because it may eliminate differences between small and large dogs in basal metabolic rate and physiologic determinants such as drug distribution, metabolism, and excretion; however, this dosing method may not be appropriate for all drugs and patients because of variations in breed, age, and disease.[48]

The dose-limiting toxic effects of carboplatin in tumor-bearing dogs are neutropenia and thrombocytopenia.[21] Because carboplatin is excreted by the kidneys, dogs with renal insufficiency may have prolonged half-life and delayed drug elimination.[21,49] Gastrointestinal toxicosis in dogs receiving carboplatin is directly correlated with initial serum urea nitrogen and creatinine concentrations.[20] Unfortunately, neither complete pretreatment serum biochemical information nor hematologic changes after treatment could be determined from retrospective analysis of records in the study reported here. Overall, gastroenteritis after treatment with carboplatin was uncommon; 89 treatments were administered, and adverse effects developed after 7. However, 2 dogs required hospitalization, and 1 dog was subsequently euthanatized. For this reason, prophylactic gastrointestinal protectants should be considered when small dogs are treated. Additionally, modification of carboplatin dose should be considered for dogs with renal insufficiency.

Systemic therapy may be an appropriate adjunct to local treatment for dogs with malignant melanomas. In the study reported here, carboplatin did have activity against measurable tumors.

[a]Paraplatin, Bristol-Myers Squibb Co, Princeton, NJ.
[b]Systat, version 9.0, SPSS Inc, Chicago, Ill.

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Appendix

Criteria* for grading toxic effects in dogs treated with carboplatin

Toxic effect	Grade
Anorexia	
None	0
Inappetance	1
Anorexia, duration < 3 d	2
Anorexia, duration ≥ 3 to < 5 d	3
Anorexia, duration ≥ 5 d; 10% weight loss	4
Vomiting	
None	0
Nausea	1
Sporadic, self-limiting	2
1-5 episodes/d, < 2 d	3
6-10 episodes/d, requires hospitalization	4
Diarrhea	
None	0
Soft feces, responds to dietary modification	1
1-4 watery feces/d, < 2 d	2
4-7 watery feces/d or > 2 d	3
> 7 watery feces/d or bloody, requires hospitalization	4

*Modified from Eastern Cooperative Oncology Group.[50]