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## Clinical effects of vinorelbine administration in the management of various malignant tumor types in dogs: 58 cases (1997–2012)

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### Abstract

**Objective**—To evaluate the effectiveness of vinorelbine in the management of various malignant tumor types in dogs.

**Design**—Retrospective case series.

**Animals**—58 dogs with malignant tumors, including pulmonary carcinoma (n = 31), histiocytic sarcoma (9), mast cell tumor (5), lymphoma (4), melanoma (2), and 7 other tumor types (1 each).

**Procedures**—Medical records of dogs treated with vinorelbine from December 1997 to December 2012 were reviewed for data regarding signalment, clinical signs, physical examination findings, clinicopathologic test results, diagnostic imaging results, vinorelbine doses and dose frequency, surgery and radiotherapy details when applicable, other chemotherapeutics administered, and outcomes. Descriptive, comparative, and survival statistics were computed for all dogs and for dogs by histologic subgroup of tumors.

**Results**—Vinorelbine was administered palliatively to 44 (76%) dogs. One (2%) dog had a complete response for 162 days, 5 (11%) dogs had a partial response for a median duration of 91 days, 19 (43%) dogs had stable disease for a median duration of 68 days, and 19 (43%) dogs developed progressive disease after a median duration of 21 days. Clinical benefit was more difficult to assess in the remaining 14 (24%) dogs that received vinorelbine as an adjuvant treatment. Overall median time to tumor progression was 103 days (range, 5 to 1,533 days).

**Conclusions and Clinical Relevance**—Vinorelbine appeared to be effective in the treatment of several tumor types in dogs. Follow-up prospective studies of the clinical benefit of the drug in specific clinical scenarios will be necessary to support this conclusion.

Vinorelbine tartrate (3',4'-didehydro-4'-deoxy-C'-norvincaloblastine) is a semisynthetic derivative of the vinca alkaloid vinblastine (5'-nonhydrovinblastine).<sup>1,2</sup> Like the more well-recognized vinca alkaloids, vinorelbine's major mechanism of antitumor activity is

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disruption of the structure and function of cellular mitotic spindles. This is reflected in failure of cell division at metaphase. In addition to its anti-mitotic spindle activity, vinorelbine may also interfere with amino acid and protein metabolism, cAMP metabolism, glutathione metabolism, calmodulin-dependent calcium transport ATPase activity, cellular respiration, nucleic acid biosynthesis, or lipid biosynthesis.<sup>1,2</sup>

In humans, the typical dosage regimen for vinorelbine as a sole treatment is 30 mg/m<sup>2</sup> administered IV weekly or every 2 weeks until tumor progression or adverse events become a concern. When the drug is administered in conjunction with cisplatin, the dosage is 25 mg/m<sup>2</sup>, IV, weekly, until the same endpoints. Weekly hematologic monitoring is required. Dose adjustments are usually made on the basis of hematologic, gastrointestinal, or hepatotoxic effects that develop.<sup>1</sup>

The adverse-event profile of vinorelbine in humans is similar to that of other vinca alkaloids and includes myelosuppression, which is manifested predominantly as neutropenia, and gastrointestinal disturbances such as nausea, vomiting, diarrhea, and constipation.<sup>1</sup> Less commonly reported adverse events include fatigue, alopecia, mild to moderate peripheral neuropathy, jaw pain, myalgia, arthralgia, hemorrhagic cystitis, and inappropriate antidiuretic hormone secretion.<sup>1</sup> Vinorelbine also causes thrombophlebitis or moderate tissue necrosis following inadvertent extravasation of the drug.<sup>1</sup> Additionally, in humans undergoing radiotherapy, vinorelbine may act as a radiation sensitizer.<sup>1</sup>

Pharmacological data on vinorelbine in dogs were published in 1993<sup>3</sup>; however, clinical experience with vinorelbine in veterinary oncology has been limited. Findings of a phase 2 clinical trial<sup>4</sup> resulted in the recommendation that 15 mg/m<sup>2</sup> be used as a starting dose for vinorelbine in dogs, with neutropenia identified as the dose-limiting toxic effect (ie, adverse event that most often limits additional increases in the dose of the chemotherapeutic agent). In that study,<sup>4</sup> myelosuppression was detected in 6 of 19 (32%) treated dogs and grade 2 to 4 neutropenia in 4 (21%) dogs that received doses in excess of 15 mg/m<sup>2</sup>. In 2 subsequent studies, clinically relevant neutropenia (grade 2 to 4) was identified in 9 of 24 (38%) dogs treated with vinorelbine<sup>5</sup> (15 mg/m<sup>2</sup>) and after 8 of 89 (9%) total administered doses given to 14 dogs receiving a median of 6 doses (range, 1 to 16 doses) at a median of 15 mg/m<sup>2</sup> (range, 9 to 18 mg/m<sup>2</sup>).<sup>6</sup> Gastrointestinal toxicosis was identified in only 16% of dogs receiving vinorelbine in one of the aforementioned studies,<sup>4</sup> whereas the other studies revealed mild to moderate gastrointestinal toxic effects in 11 of 24 (46%) treated dogs<sup>5</sup> or after 44 of 89 (49%) total administered doses.<sup>6</sup> A dose of 11.5 mg of vinorelbine/m<sup>2</sup> has been recommended as the starting dose in cats on the basis of findings in a phase 1 clinical trial,<sup>7</sup> with dose-limiting adverse events including neutropenia, vomiting, and nephrotoxic effects.

In the United States, vinorelbine has been approved by the FDA for use alone or in combination with cisplatin for treatment of humans with advanced-stage non-small-cell lung cancer.<sup>1</sup> In other countries, the drug has also been approved for treatment of advanced breast cancer.<sup>1,2</sup> Moreover, evidence exists to support the use of vinorelbine in the management of a wide spectrum of cancers in humans, including cervical cancer,<sup>8</sup> ovarian cancer,<sup>9</sup> head and neck cancers,<sup>10</sup> esophageal squamous cell carcinoma,<sup>11</sup> mesothelioma,<sup>12</sup> multiple

myeloma,<sup>13</sup> Hodgkin and non-Hodgkin lymphoma,<sup>14,15</sup> and pediatric brain tumors.<sup>16</sup> Vinorelbine is considered particularly promising for advanced-stage cancers in humans treated previously with vinca alkaloids because complete cross-resistance has not been reported for either of the more commonly administered vinca alkaloids (ie, vincristine and vinblastine).<sup>1</sup>

Clinical activity of vinorelbine has been identified in several dogs with bronchoalveolar carcinoma<sup>4</sup> as well as dogs with naïve mast cell disease or refractory transitional cell carcinoma of the urinary bladder.<sup>5,6</sup> The objective of the study reported here was to determine the effectiveness of vinorelbine for treatment of dogs with various types of malignant tumors.

## Materials and Methods

### Case selection

A search of pharmacy records at the University of Wisconsin Veterinary Medical Teaching Hospital was performed to identify dogs for which a diagnosis of malignant tumors had been made from December 1997 to December 2012 and for which vinorelbine<sup>a</sup> had been prescribed. Dogs may have received vinorelbine as postoperative adjuvant treatment when they had unappreciable or microscopically evident disease or as palliative treatment when they had primary or progressive macroscopically evident disease.

For a dog to be included in the study, its medical record was required to contain a thorough medical history, results of a complete physical examination, and data on diagnostic testing and staging suitable to the diagnosis or presumptive diagnosis as well as appropriate and adequate monitoring, cancer restaging, and follow-up information. Appropriateness and adequacy of monitoring, cancer restaging, and follow-up information were decided on a case-by-case basis by an oncology resident and board-certified veterinary oncologist, with consideration of the diagnosis, extent of therapeutic interventions, and response to treatment. Essentially, medical records were required to contain information on the outcome for each dog as well as the dog's response to vinorelbine. Dogs were excluded when their medical records lacked adequate information.

### Medical records review

Information retrieved from the medical records included signalment, clinical signs, relevant physical examination findings, clinicopathologic test results (hematologic evaluation, serum biochemical analysis, urinalysis, cytologic evaluation, or histologic evaluation), diagnostic imaging results (radiography, ultrasonography, CT, and MRI), vinorelbine dosage, and details for surgery, radiotherapy, or other treatments. Referring veterinarians and owners were contacted when additional information was required. Information obtained from the referring veterinarians or owners predominantly pertained to follow-up and outcomes.

Responses of solid tumors were retrospectively evaluated and categorized in accordance with the VCOG consensus statement on response evaluation criteria in solid tumors,<sup>17</sup> on the

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<sup>a</sup>Navelbine, Pierre Fabre Pharmaceuticals Inc, Parsippany, NJ.

basis of absolute or diagnostic-imaging measurements of longest tumor diameter and subsequent variations in these measurements. To be classified as a response, changes in solid tumor size were required to have been documented for a minimum period of 28 days.

Responses of nonsolid tumors (ie, lymphoma) were also retrospectively evaluated and categorized in accordance with the published response evaluation criteria of the VCOG for peripheral nodal lymphoma in dogs.<sup>18</sup> To be classified as a response, changes in lymph node size were required to have been maintained for a minimum period of 7 days, given that most dogs received vinorelbine once per week and all dogs with lymphoma had advanced-stage refractory disease. A clinical response was defined as resolution of all evidence of disease, with all lymph nodes considered unremarkable in size. A partial response was defined as at least a 30% decrease in the mean sum of the longest diameters of the target lymph nodes, with the mean sum of the longest diameters of the target lymph nodes at baseline used as reference. Progressive disease was defined as at least a 20% increase in the mean sum of the longest diameters of the target lymph nodes, with the mean sum of the longest diameters of the target lymph nodes at baseline used as reference, or the appearance of new lesions (eg, in the liver, spleen, or bone marrow). Stable disease was defined as any variation in lymph node size not sufficient to qualify as a partial response or progressive disease.

Toxic effects were retrospectively graded by use of the common terminology criteria of the VCOG for adverse events following chemotherapy or biologic antineoplastic treatment in dogs and cats.<sup>19</sup> Grading was performed on the basis of each dog's detailed medical record, which included a quality-of-life survey for each hospital visit during chemotherapy.

### Statistical analysis

Descriptive statistics were calculated to characterize the dogs as a group and by histologic subgroups of tumor and the vinorelbine dosing regimens. Two measures of outcome were evaluated for all dogs and for dogs by histologic subgroups of tumor. Time to tumor progression was defined as the interval from the date on which vinorelbine treatment began until the date of confirmed disease progression (local recurrence or metastatic disease). Overall survival time was defined as the number of days from date of first diagnosis until date of death (regardless of whether death was attributable to the primary neoplasia or another cause). Data were considered right censored at the time of last veterinary contact if the dogs remained alive at the conclusion of the study period or if they were ultimately lost to follow-up. Kaplan-Meier survival analysis was performed for both outcome measurements when appropriate, to generate median TTP and OST in various conditions, and the log-rank test was used to then compare these outcome measurements between groups. Cox proportional hazard regression analysis was used to identify associations between potential confounding factors and outcome measurements. Statistical comparison of outcomes between dogs (specifically those with primary pulmonary carcinoma) that underwent surgery and then did or did not receive chemotherapeutic agents, however, was not possible within the scope of the study. All statistical analyses were performed with 2 commercially available software packages.<sup>b,c</sup>

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<sup>b</sup>Excel for Mac, version 14.2.5, Microsoft Corp, Redmond, Wash.

<sup>c</sup>R for Mac OS X GUI 2012, version 2.15.2, R Foundation for Statistical Computing, Vienna, Austria.

## Results

### Dogs

From December 1997 to December 2012, 60 dogs were identified with malignant tumors and had a prescription for vinorelbine in their medical record. Of these dogs, 58 (97%) fulfilled the study inclusion criteria. Two dogs were excluded because they were immediately lost to follow-up. Median age of included dogs was 10.0 years (range, 3.3 to 16.5 years). Thirty-four (59%) dogs were spayed females, 3 (5%) were sexually intact females, 19 (33%) were castrated males, and 2 (3%) were sexually intact males. Twenty-six breeds were represented as follows: Labrador Retriever and Labrador Retriever crosses, 13 (22%); Golden Retriever and Golden Retriever crosses, 8 (14%); Cocker Spaniel and Cocker Spaniel crosses, 5 (9%); German Shepherd Dog, 4 (7%); Bernese Mountain Dog, 3 (5%); Rottweiler, Flat-Coated Retriever, Boxer, and Miniature Schnauzer, 2 (3%) each; and 17 other breeds, 1 (2%) each. Median body weight for all dogs was 28.1 kg (61.8 lb), with a range of 5.0 to 66.0 kg (11 to 145.2 lb).

Twelve histologic types of tumor were represented as follows: primary pulmonary carcinoma, 31 (53%); histiocytic sarcoma, 9 (16%); mast cell tumor, 5 (9%); lymphoma, 4 (7%); melanoma, 2 (3%); and apocrine gland anal sac adenocarcinoma, mammary gland adenocarcinoma, thyroid gland carcinoma, tonsillar squamous cell carcinoma, metastatic carcinoma of unknown primary site of origin, osteosarcoma, and soft tissue sarcoma, 1 (2%) each. Forty-two (72%) diagnoses were made on the basis of histologic findings and 14 (24%) on the basis of cytologic findings; 2 (3%) diagnoses were made presumptively on the basis of results of diagnostic imaging.

### Administration and toxicosis profile

Median dose of vinorelbine was 15 mg/m<sup>2</sup> (range, 8 to 22 mg/m<sup>2</sup>), IV. Median number of doses administered was 4 (range, 1 to 19), with a median cumulative dose of 78 mg/m<sup>2</sup> (range, 12 to 248 mg/m<sup>2</sup>). Forty-five (78%) dogs received vinorelbine weekly. In 12 (21%) dogs, each of which received > 4 doses, the frequency of administration was extended to every 2 weeks for logistic reasons. In 1 (2%) dog, the administration interval was extended to every 2 weeks as a result of myelosuppression arising with weekly administration.

Vinorelbine was administered palliatively to dogs with macroscopically evident disease in most situations (n = 44 [76%]). Only 14 (24%) dogs received vinorelbine as an adjunct treatment when they had no appreciable disease or had only microscopically appreciable disease. Of these 14 dogs, 13 had primary pulmonary tumors, and 1 had a recurrent grade 2 mast cell tumor that was then excised a second time.

All dogs receiving vinorelbine were initially evaluated on a weekly basis, including hematologic testing. The most commonly reported adverse event associated with vinorelbine administration was neutropenia, which was reported for 23 (40%) dogs. Overall, 6 (10%) dogs had grade 4 neutropenia, of which 2 were febrile; 5 (9%) dogs had grade 3 neutropenia, of which 2 were also febrile; 8 (14%) dogs had grade 2 neutropenia; and 4 (7%) dogs had grade 1 neutropenia. Dose administration was delayed and the dose reduced by 10% to 25% for 12 (20%) dogs as a result of myelosuppression. Treatment was stopped for the 2 dogs

with grade 4 neutropenia and fever. One dog became febrile after receiving the first dose of vinorelbine without becoming neutropenic. No association was detected between magnitude of the vinorelbine dose and grade of neutropenia ( $P = 0.07$ ), nor was there an association between timing of the dose and neutropenic or febrile episodes ( $P = 1.00$ ).

Thrombocytopenia was detected in 4 (7%) dogs, 3 (5%) of which had grade 2 thrombocytopenia and 1 (2%) of which had grade 1 thrombocytopenia. No association between dose and grade of thrombocytopenia was identified ( $P = 0.50$ ). Twelve (20%) dogs developed mild gastrointestinal toxic effects, including inappetence, transient vomiting, and diarrhea. One dog developed nonspecific signs of abdominal pain and had increases in liver enzyme activities. These effects were not investigated further, and that dog recovered with supportive treatment based on clinical signs, including analgesia and a delay in dose administration. One dog developed bilateral hind limb ataxia after receiving a third dose of vinorelbine (15, 16.5, and then 18 mg/m<sup>2</sup> [cumulative dose, 49.5 mg/m<sup>2</sup>]), and no additional doses were administered. One dog developed diffuse epidermal crusting with ulcerated and exudative lesions 4 days after receiving the second dose of vinorelbine and received no additional doses. Twenty-three (40%) dogs did not have an adverse event associated with vinorelbine administration.

### Overall outcome

Median duration of follow-up was 262 days (range, 5 to 1,264 days; mean, 370 days). Of the 44 (76%) dogs with gross measurable disease at the time of vinorelbine administration, 1 (2%) had a complete response, documented after the third weekly dose of vinorelbine had been given, for a duration of 162 days; 5 (11%) had a partial response for a median duration of 91 days (range, 21 to 771 days); 19 (43%) had stable disease for a median duration of 68 days (range, 35 to 300 days); and 19 (43%) had progressive disease for a median duration of 21 days (range, 8 to 43 days). For the 14 (24%) dogs that received vinorelbine as an adjuvant treatment, median TTP was 103 days (range, 5 to 1,533 days).

### Primary pulmonary carcinoma

Thirty-one of 58 (53%) dogs had primary pulmonary carcinoma. Several histologic subtypes were represented in this subgroup, including bronchioloalveolar (bronchogenic) adenocarcinoma ( $n = 8$  [3% of all pulmonary carcinomas]), papillary adenocarcinoma (7 [23%]), unclassified pulmonary carcinoma (10 [32%]), squamous cell carcinoma (1 [3%]), and pulmonary carcinosarcoma (1 [3%]). Four primary lung tumors had epithelial characteristics that were not assigned a more specific histologic or cytologic classification.

Median age of dogs with primary pulmonary carcinoma was 11.0 years (range, 7.8 to 16.5 years). Twenty-one (68%) dogs were spayed females, and 10 (32%) were castrated males. Seventeen breeds were represented, including Labrador Retriever and Labrador Retriever crosses (8 [26%]), Cocker Spaniel and Cocker Spaniel crosses (4 [13%]), Golden Retriever and Golden Retriever crosses (3 [10%]), Boxer (2 [6%]), Bernese Mountain Dog (2 [6%]), and 12 other breeds (1 [3%] each). Median body weight for the dogs was 22.2 kg (48.8 lb) with a range of 6.8 to 42.2 kg (15.0 to 92.8 lb).

Fifteen (48%) dogs with primary pulmonary carcinoma underwent lung lobectomy as the primary treatment. Nine of those dogs had concurrent regional lymph node extirpation. Lymph node metastasis was confirmed histologically in 3 dogs and suspected in another 2 dogs. Surgical margins were considered incomplete in 3 dogs, and 2 dogs had malignant pleural effusion at the time of lobectomy.

Of the 15 dogs that underwent surgery, 13 (with no appreciable or microscopically evident disease) received vinorelbine as first-line adjuvant treatment. One dog concurrently received piroxicam. Another dog received multiple chemotherapeutic agents prior to vinorelbine administration, which included carboplatin, doxorubicin, cyclophosphamide, paclitaxel, dolastatin, gemcitabine, endostatin, and docetaxel. Vinorelbine had been administered while that dog had progressive disease. One dog with progressive disease received no initial adjuvant treatment, and vinorelbine was then administered after progressive disease was diagnosed. During the study period, adjuvant treatment was provided to owners as an option for all dogs with primary lung tumors undergoing lung lobectomy at the teaching hospital. The recommendation made and the agents selected were at the discretion of the clinician and might have been impacted by clinical findings, including histologic subtype, stage, and grade of the tumors, although ultimately the decision to provide such treatments was made by dog owners.

For all 15 dogs that underwent surgery initially, with or without immediate adjuvant treatment, median TTP was 95 days (range, 5 to 1,533 days), and median OST was 415 days (range, 22 to 2,003 days). For the 13 dogs that received immediate adjuvant treatment with vinorelbine, median TTP was 103 days (range, 5 to 1,533 days), and median OST was 324 days (range, 22 to 2,003 days). These values were not significantly different from those of all 15 dogs that underwent surgery ( $P=0.55$  and  $P=0.61$ , respectively). Outcomes were not compared between dogs that underwent surgery and then did or did not receive chemotherapeutic agents because this was not possible within the scope of the study.

Sixteen (52%) dogs with macroscopically evident primary pulmonary carcinoma had no initial surgery but received vinorelbine. In 10 dogs, surgery was not performed because confirmation or suspicion of metastatic disease existed at the time of diagnosis. Five other dogs had other tumors, including appendicular osteosarcoma ( $n=1$ ), high-grade soft tissue sarcoma (1), lymphoma (1), urinary bladder carcinoma with regional lymph node metastasis (1), and grade III metastatic mast cell tumor (1), that complicated the clinical scenario. For the remaining dog, the owner made the decision that the dog would not undergo surgery.

For 12 of the 16 dogs with macroscopically evident primary pulmonary carcinoma, vinorelbine was the primary palliative treatment. The other 4 dogs with macroscopically evident pulmonary carcinoma received treatment with multiple chemotherapeutic agents prior to receiving vinorelbine, which included cisplatin, carboplatin, cyclophosphamide, doxorubicin, and piroxicam. One of these dogs also received treatment with a genetically modified *Salmonella enterica* serotype Typhimurium bacterium (VNP20009) prior to vinorelbine administration. Following palliative administration of vinorelbine alone or following other treatments, 3 dogs had a partial response for a median duration of 91 days (range, 47 to 181 days), 7 had stable disease for a median duration of 68 days (range, 52 to

300 days), and 6 had progressive disease for a median of 21 days (range, 8 to 32 days). No dogs with primary pulmonary tumors had a complete response following palliative treatment with vinorelbine. Median TTP and OST were 55 days (range, 8 to 300 days) and 92 days (range, 8 to 767 days), respectively.

In the 2 dogs that initially underwent surgery but had local recurrence or metastatic disease prior to commencing vinorelbine as a palliative treatment, stable disease was documented for a period of 91 and 48 days, respectively. When these 2 dogs were included with the aforementioned 16 dogs that received palliative-intent treatment for macroscopically evident disease, then 9 dogs had stable disease with a median duration of 68 days (range, 48 to 300 days). Median TTP and OST were 55 days (range, 8 to 300 days) and 101 days (range, 8 to 1,019 days), respectively. These outcomes were not significantly ( $P = 0.94$  and  $P = 0.07$ ) different, compared with respective outcomes for the 16 dogs treated palliatively with vinorelbine without any prior surgery. Only 5 dogs with primary pulmonary carcinoma received additional treatment after vinorelbine, which included carboplatin and lomustine (*N*-[2-chloroethyl]-*N*'-cyclohexyl-*N*-nitrosourea).

### Histiocytic sarcoma

Nine dogs with histiocytic sarcoma were treated with vinorelbine. Median age in this subgroup was 7.0 years (range, 5.7 to 13.1 years). Five dogs were spayed females, 3 were castrated males, and 1 was a sexually intact male. Breeds represented included Flat-Coated Retriever ( $n = 2$ ) and Bernese Mountain Dog, Rottweiler, Golden Retriever, German Shepherd Dog, Siberian Husky, Poodle cross, and Miniature Schnauzer (1 each). Median body weight was 30.6 kg (67.3 lb) with a range of 8.2 to 43.6 kg (18.0 to 95.9 lb).

Only 2 dogs had appendicular (cubital [elbow] joint and tibial) histiocytic sarcoma. Both had evidence of metastasis at the time of diagnosis and received palliative treatment only. Three dogs had primary pulmonary lesions, and all 3 underwent lung lobectomy. Two dogs had subcutaneous lesions, with one in the area of the left prescapular lymph node and the other in the ventral cervical region (perhaps effaced and enlarged and therefore displacing the retropharyngeal lymph node or mandibular lymph node). Both lesions were presumed to be metastatic, although no primary tumor was identified, and both were extirpated initially. One dog had primary splenic disease and underwent splenectomy as the primary treatment. The other had primary ocular disease, and enucleation was the initial treatment.

Vinorelbine was administered palliatively to all 9 dogs. Seven dogs had undergone surgery and received lomustine as an adjuvant prior to receiving vinorelbine for treatment of progressive or recurrent disease. One dog with multiple pulmonary metastases at the time of diagnosis and another dog with diffuse metastases to intra-abdominal lymph nodes at the time of diagnosis had received lomustine as the primary palliative treatment prior to receiving vinorelbine for treatment of progressive disease.

The dog with a primary lesion in the elbow joint and suspected metastatic pulmonary disease (not confirmed histopathologically) received 17 doses of vinorelbine (initially at weekly intervals and then every 2 weeks). A partial response was evident radiographically for the pulmonary lesions 36 days after receiving the initial dose of vinorelbine, and complete



resolution of the pulmonary lesions was radiographically evident 91 days after that initial dose, with an overall TTP of 771 days. Measurements of the primary lesion in the elbow joint revealed a decrease in lesion size after treatment, but the associated musculoskeletal changes did not completely resolve. In another dog with a primary splenic lesion, the lesion was surgically removed, but the dog then developed pulmonary metastasis. That dog had evidence of progressive disease while receiving lomustine, but then had a radiographically apparent complete response 21 days after weekly treatments with vinorelbine began. It received 19 total doses of vinorelbine, with 6 administered once per week, 7 given once every 2 weeks, then another 6 given once per week, and had a TTP of 162 days. The final 6 weekly doses were administered after progressive disease was documented, and these doses resulted in a partial response for a duration of an additional 50 days. Four other dogs had stable disease for a median TTP of 61 days (range, 35 to 217 days). In 2 of those dogs, progressive disease was detected within 12 to 27 days after vinorelbine treatment began, after which the dogs were euthanized. Another dog that received 4 doses of vinorelbine at weekly intervals had evidence of progressive disease 28 days after treatment began.

### **Mast cell disease**

Five dogs with mast cell disease were treated with vinorelbine. Median age of this subgroup was 8.2 years (range, 6.7 to 8.9 years). Three were spayed females, 1 was a castrated male, and 1 was a sexually intact male. There were 2 Labrador Retrievers and 1 each of Labrador Retriever cross, Golden Retriever, and Shih Tzu. Median body weight was 34.6 kg (76.1 lb), with a range of 5.0 to 66.0 kg.

In all dogs, high-grade mast cell tumors had been diagnosed on the basis of histopathologic findings and biological behavior of the tumors. Four dogs had confirmed evidence of regional lymph node metastasis when vinorelbine administration started; in the fifth dog, lymph node involvement was suspected in addition to the confirmed presence of local disease recurrence.

All dogs had received vinblastine and prednisolone prior to vinorelbine administration as well as various combinations of lomustine, cyclophosphamide, masitinib, and toceranib phosphate.<sup>d</sup> Vinorelbine was administered palliatively to 4 dogs, whereas 1 dog had undergone a third surgery to excise a recurrent lesion immediately before vinorelbine administration began.

Two dogs received only 1 dose of vinorelbine, and progressive disease was evident shortly thereafter. One dog underwent a third cytoreductive surgery followed by 3 doses of vinorelbine, although the third dose was administered because of rapid local recurrence. One dog developed crusting, ulcerated, and erosive skin lesions 4 days after the second dose was administered and received no additional treatment. Histologic evaluation was not performed; therefore, the exact etiology of these lesions could not be ascertained. One dog received 8 doses of vinorelbine and had stable disease for 87 days.

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<sup>d</sup>Palladia, Pfizer Inc, New York, NY.

## Multicentric lymphoma

Four dogs with multicentric lymphoma were treated with vinorelbine. Median age of this subgroup of dogs was 5.1 years (range, 3.3 to 8.8 years). Two were sexually intact females and 2 were castrated males. There were 2 Golden Retrievers, 1 German Shepherd Dog, and 1 American Staffordshire Terrier. Median body weight was 29.2 kg (64.2 lb), with a range of 22.6 to 33.6 kg (49.7 to 73.9 lb). All dogs had advanced-stage multicentric lymphoma. Two dogs had B-cell lymphoma, 1 dog had T-cell lymphoma, and 1 dog had mixed B-cell and T-cell lymphoma.

Vinorelbine was administered as a rescue medication to all 4 dogs with multicentric lymphoma. All dogs had received multiple chemotherapeutic agents prior to vinorelbine treatment, including a protocol involving cyclophosphamide, doxorubicin, vincristine, and prednisone, followed by several other rescue medications and protocols. Two dogs (one with T-cell and the other with mixed B- and T-cell lymphoma) received only 1 dose of vinorelbine, and progressive disease was detected 8 and 17 days later, soon after which the dogs were euthanized. One dog with stage IIIa multicentric B-cell lymphoma received 4 doses of vinorelbine and had a short-lived partial response for 21 days. A second dog with stage IIIa multicentric B-cell lymphosarcoma received 8 doses of vinorelbine and had stable disease for 56 days.

## Other tumors

Two dogs with melanoma were included in the study. In both dogs, progressive disease was evident after receiving 3 or 4 weekly doses of vinorelbine. A 9-year-old female apparent German Shepherd Dog cross had apocrine gland anal sac adenocarcinoma that was macroscopically evident and metastatic. The dog had previously undergone surgery and treatment with other drugs (mitoxantrone, paclitaxel, and carboplatin) before receiving 12 doses of vinorelbine. That dog had stable disease, and more importantly, paraneoplastic hypercalcemia appeared to have resolved for 163 days after vinorelbine administration began.

A 4-year-old castrated male Labrador Retriever with thyroid gland carcinoma and pulmonary metastasis at the time of initial diagnosis had previously received doxorubicin and then carboplatin. The dog subsequently received 10 doses of vinorelbine, and it had stable disease for 123 days after vinorelbine administration began.

A 10-year-old spayed female Labrador Retriever cross with metastatic mammary gland carcinoma had undergone mastectomy and received doxorubicin before vinorelbine treatment began. The dog received a predetermined finite course of treatment involving 4 doses of vinorelbine, and it had stable disease for 109 days after the treatment began.

One dog with metastatic carcinoma of unknown primary site received 4 weekly doses of vinorelbine and had evidence of progressive disease 29 days after that treatment began. Another dog with metastatic tonsillar squamous cell carcinoma received a dose of vinorelbine once every 1 to 2 weeks for 5 doses and had evidence of progressive disease 33 days after that treatment began. A 7-year-old spayed female American Water Spaniel had metastatic grade 3 soft tissue sarcoma. The affected limb was amputated, and the dog

received adjunctive treatment with doxorubicin, followed by treatment with toceranib phosphate and then metronomic treatment with cyclophosphamide and piroxicam. That dog had evidence of progressive disease documented 28 days after commencing weekly vinorelbine treatment. A 7-year-old spayed female Rottweiler cross had a metastatic appendicular osteosarcoma. The affected limb was amputated, which was followed by cisplatin and doxorubicin treatment. That dog had progressive disease documented 21 days after commencing weekly vinorelbine treatment.

## Discussion

Findings of the present study supported the preexisting hypothesis that vinorelbine has clinical activity against primary lung tumors in dogs. In a previous study<sup>4</sup> in which the effects of vinorelbine treatment were evaluated in 7 dogs with measurable bronchioloalveolar carcinoma, a partial response was identified in 2 dogs, and stable disease was achieved in an additional 3 dogs. In the present study, vinorelbine treatment resulted in a partial response in 3 of 18 dogs with macroscopically evident pulmonary carcinoma and stable disease in an additional 9 dogs with the same histologic tumor type. The median OST of 324 days for dogs treated with vinorelbine as an adjuvant treatment in the present study is comparable to median OSTs of 106, 361, and 120 days achieved in earlier studies<sup>20–22</sup> for dogs with primary pulmonary neoplasia that were treated primarily with surgery alone, without adjuvant treatment with vinorelbine. However, given the marked differences among the previous studies<sup>20–22</sup> and the study reported here with respect to design, treatments evaluated, data collected and reported, and statistical analyses, comparison of any findings must be made with caution, particularly given that vinorelbine was not one of the chemotherapeutic agents administered in 2 of those studies.<sup>21,22</sup> Ideally, a controlled clinical trial should be conducted to evaluate whether adjunctive administration of vinorelbine would result in improved outcomes in dogs with primary pulmonary neoplasia, compared with outcomes for dogs undergoing surgery alone.

Findings related to the 9 dogs with histiocytic sarcoma in the present study also appeared encouraging. It has been stated that any therapeutic intervention, beyond analgesia and prednisolone alone, is capable of improving outcomes in dogs with histiocytic sarcoma.<sup>23</sup> The most effective treatment regimen has yet to be established. A previous study<sup>24</sup> involving 56 dogs with macroscopically evident or disseminated disease revealed an overall response rate of 46% in those treated with lomustine, with 54% of dogs that lived > 7 days following the first treatment achieving a partial or complete response. Median TTP in that study<sup>24</sup> was 85 days, and median OST was 172 days. A longer median OST (568 days) has been reported for dogs with appendicular histiocytic sarcoma managed with an aggressive multimodal treatment approach.<sup>25</sup> In the present study, a complete response to vinorelbine administration was identified in 1 dog with metastatic splenic histiocytic sarcoma, with a TTP of 162 days and OST of 277 days. A prolonged partial response was identified in a second dog with an appendicular primary tumor and subsequent pulmonary metastases, with a TTP of 771 days and OST of 1,264 days. Stable disease was observed in 4 dogs (3 with metastatic pulmonary histiocytic sarcoma and 1 with an unidentified primary tumor). Meaningful statistical analysis could not be performed because of the small sample size.

Effects of vinorelbine have been investigated in dogs with naïve cutaneous mast cell disease. In a phase 2 clinical trial,<sup>5</sup> an overall response rate of 13% was achieved in 24 dogs with mast cell disease treated with vinorelbine. Because only 5 dogs with mast cell disease were included in the present study, meaningful statistics could not be calculated. Given a 20% response rate for palliative administration, we suggest that vinorelbine might be considered a reasonable rescue agent for mast cell disease in dogs that is unresponsive to preferred first-line chemotherapeutic agents, such as vinblastine and toceranib phosphate.

Among the 4 dogs with multicentric lymphoma included in the present study, 1 dog with stage IIIa multicentric B-cell lymphoma received 4 doses of vinorelbine and had a partial response for 21 days. A second dog with stage IIIa multicentric B-cell lymphosarcoma received 8 doses, and it had stable disease for 56 days. The partial response detected in the first dog was admittedly short-lived, but maintenance of stable disease in the second dog for 56 days might be considered a satisfactory outcome in this subset of dogs with lymphoma. In dogs with advanced-stage refractory disease that are otherwise clinically normal, vinorelbine might be considered a reasonable rescue agent.

Dose and administration regimens for most dogs of the present study were similar to those reported for vinorelbine in dogs of other studies.<sup>4-6</sup> Not surprisingly, therefore, the adverse event profile was also similar to the adverse event profiles identified in those studies. Neutropenia developed in 23 of 58 (40%) dogs in the present study, compared with 13 of 24 (54%) dogs in one study<sup>5</sup> and after 19 of 89 (21%) doses in another study.<sup>6</sup> Four of the neutropenic dogs in the present study had concurrent fever; in all affected dogs, fever and neutropenia resolved with treatment. Concurrent fever and neutropenia has been recognized in only 1 of the 57 dogs reported to have received vinorelbine in the veterinary literature<sup>4-6</sup> and in only 1 of the 19 cats in the phase 1 dose-determination trial.<sup>7</sup>

Four (7%) dogs developed clinically irrelevant thrombocytopenia in the present study. Three of these dogs had grade 2 thrombocytopenia, and 1 dog had grade 1 thrombocytopenia. An association between vinorelbine dose and thrombocytopenia grade was not established ( $P=0.50$ ), but thrombocytopenia did appear to worsen with an increasing number of doses of vinorelbine. This finding adds weight to the assertion of other investigators<sup>4</sup> that vinorelbine-induced myelosuppression might be cumulative. Twelve (21%) dogs had mild gastrointestinal upset after receiving vinorelbine. One dog had nonspecific signs of abdominal pain and increases in liver enzyme activities that were not investigated further, and that dog recovered with supportive treatment. One dog developed bilateral hind limb ataxia following a third dose of vinorelbine (cumulative dose, 49.5 mg/m<sup>2</sup>), which was presumed to be peripheral neuropathy attributable to treatment with vinca alkaloids, although confirmatory electromyography was not performed.

The dog that developed diffuse crusting, ulcerating, and exudative skin 4 days after the second dose of vinorelbine was administered was included in an earlier vinorelbine dose-evaluation study.<sup>3</sup> That dog had a metastatic mast cell tumor, and although the skin lesions were considered consistent with those that might develop with a drug reaction (toxic epidermal necrolysis), they may also have been indicative of progressive mast cell disease. Necropsy was not performed, and the etiology of the skin condition was not confirmed.

Several limitations were inherent to the retrospective approach to data collection in the present study. Multiple clinicians were involved in case management and clinical decision making over an extended period. Consequently, no standardized procedures were in place for confirmation of histologic or cytologic diagnosis, staging and restaging of disease, performance of monitoring examinations, documentation of responses, grading of toxic effects, and modifications of doses. Furthermore, no exclusion criteria were in place for the number and type of medications used prior to the administration of vinorelbine, the number and type of medications administered concomitantly, or any treatments given following vinorelbine administration. The data generated from this study would therefore rank low in the hierarchy of evidence quality used in evidence-based medicine.<sup>26</sup> Nevertheless, the findings would be useful in hypothesis generation to provide a basis for future studies with greater evidentiary weight, such as studies involving a contemporary control group from the same population as that from which cases were selected.

Given that the present study yielded no findings to indicate that vinorelbine dose was associated with grade or severity of adverse events, we support the previous recommendation by other investigators that 15 mg of vinorelbine/m<sup>2</sup> be used as a starting dose for vinorelbine, followed by tailoring of the dosage to minimize adverse events and maximize efficacy.<sup>4</sup> Evidence from the present and previous studies suggests that, when administered judiciously, vinorelbine may be a safe and tolerable chemotherapeutic agent in dogs that is potentially underused in veterinary oncology. The drug had ostensible antineoplastic activity in the treatment of several tumor histologic subtypes, including pulmonary carcinoma, histiocytic sarcoma, lymphoma, mast cell disease, and transitional cell carcinoma of the urinary bladder. Controlled clinical trials are needed to determine the optimal use of vinorelbine in dogs with malignant tumors.

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## Abbreviations

<b>OST</b>	Overall survival time
<b>TTP</b>	Time to tumor progression
<b>VCOG</b>	Veterinary Cooperative Oncology Group

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