Postoperative Adjuvant Treatment of Invasive Malignant Mammary Gland Tumors in Dogs with Doxorubicin and Docetaxel

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Background: Treatment outcome after surgery alone is unsatisfactory in dogs with invasive malignant mammary gland tumors.

Hypothesis: Adjuvant doxorubicin or docetaxel will improve the treatment outcome in dogs with high-risk malignant mammary gland tumors, and the use of docetaxel will be feasible in affected dogs.

Animals: Thirty-one dogs with malignant mammary gland tumors of histologic stages II and III (vascular or lymphatic invasion, regional lymph node metastasis, or distant metastasis) were used.

Methods: A prospective clinical trial in which dogs were treated with surgery alone (n = 19) or also received adjuvant chemotherapy (n = 12) with doxorubicin or docetaxel was conducted. Docetaxel was given as an IV infusion at a dose of 30 mg/m^2 preceded by dexamethasone and diphenhydramine administration.

Results: The recurrence-free interval ranged from 13 to 2,585 days (median not reached); the median metastasis-free interval and overall survival were 294 days and 370 days, respectively. Dogs treated with chemotherapy had a tendency toward higher long-term local control and survival rates, but there was no significant difference in the recurrence-free interval ($P = .17$), time to metastasis ($P = .71$), and overall survival ($P = .12$). Factors found to influence the time to metastasis and overall survival included lymph node metastasis ($P = .009$) and tumor fixation to underlying structures ($P = .043$, time to metastasis), as well as age ($P = .018$) and histologic stage ($P < .001$, survival). Mild allergic skin reactions were the most frequently observed complications of docetaxel treatment.

Conclusions and Clinical Importance: Chemotherapy did not lead to an improved outcome in this population. Docetaxel treatment was well tolerated. Additional investigations of adjuvant chemotherapy in dogs with high-risk mammary cancer are warranted.

Key words: Cancer; Canine; Chemotherapy; Mammary carcinoma; Prognosis.

Mammary tumors are among most frequent tumor types in female dogs.[1,2] Because of the protective effect of early neutering, the incidence of canine mammary tumors has decreased markedly in the United States,[2,3] however, mammary tumors still are frequently encountered in unspayed female dogs, especially in Europe.[4–7]

Surgical excision alone yields unsatisfactory results in dogs with malignant mammary tumors exhibiting lymphatic or vascular invasion because these tumors have high rates of recurrence and metastasis.[8,9] It has been revealed that within a 2-year period after surgical excision, dogs with invasive mammary tumors have a 13-fold increased risk of recurrence as compared to those with noninvasive disease.[8] The development of adjuvant treatments and the investigation of their antineoplastic efficacy, therefore, are of importance in dogs with high-risk mammary cancer.

Preclinical studies have documented the antitumor activity of doxorubicin and carboplatin in canine malignant mammary tumor cultures and of cyclophosphamide, cisplatin, and 5-fluoruracil in canine mammary tumor xenografts in severe combined immunodeficiency mice.[10,11] Adjuvant chemotherapy is routinely used in women with breast cancer, however, only limited information is available on the efficacy of postoperative chemotherapy in dogs.

Recently, a veterinary study was reported in which adjuvant chemotherapy with 5-fluoruracil and cyclophosphamide improved patient survival in comparison to dogs treated with surgery alone.[12] Also, the efficacy of doxorubicin chemotherapy for inducing partial remissions of pulmonary metastases in dogs with mammary tumors has been documented in case reports.[13,14]

In human medicine, the anthracycline doxorubicin is one of the most effective and frequently used chemotherapeutic agents in first-line adjuvant treatment of mammary carcinoma.[15,16] The taxanes are inhibitors of microtubule disassembly that result in mitotic arrest.[17] Paclitaxel and docetaxel have established efficacy in the treatment of mammary tumors in humans.[18] Docetaxel has been approved for the treatment of metastatic breast cancer since 1996, and there is increasing evidence for its beneficial effect in the treatment of early mammary carcinoma.[18–21] Taxanes, however, are not routinely used in veterinary oncology. One report describes the induction of partial remissions in 2 dogs with macroscopic mammary tumors after treatment with paclitaxel, but the overall toxicity was high.[22] To the authors' knowledge, docetaxel has not been used for the treatment of tumors in dogs. The dose of 30 mg/m^2

used in this study was derived from preclinical studies in Beagle dogs.[17] In these studies, the highest nonlethal toxic dose was found to be 30 mg/m² IV. Dose-limiting toxicity in these preclinical studies was gastrointestinal and hemotologic in nature.

The aim of this study was to investigate the efficacy of adjuvant, postoperative doxorubicin and docetaxel treatment in dogs with high-risk, invasive malignant mammary tumors in comparison to surgery alone. In addition, it was the aim of this study to document tolerance and toxicity of docetaxel in dogs with cancer.

Materials and Methods

Patient Inclusion Criteria

Dogs with mammary tumors were eligible for the study if they fulfilled the following criteria: (1) surgical excision of the mammary tumors by radical mastectomy or partial mastectomy, depending on tumor number and distribution in the mammary chain, (2) a clinical tumor stage I–IV (see the Appendix),[23] (3) histologic confirmation of malignancy in at least 1 tumor, and (4) histologic confirmation of at least 1 malignant stage II or III tumor (see the Appendix).[8] Additional inclusion criteria were no chemotherapy or radiation therapy before the study, no other serious medical illness that would limit full compliance with the study, and signed owner consent.

Pretreatment Evaluation

Dogs underwent complete clinical staging consisting of patient history, physical examination, documentation of tumor size and characteristics, CBC, serum biochemistry profile, thoracic radiographs (right and left lateral, ventrodorsal), abdominal radiographs (lateral), abdominal ultrasound, ECG, and an echocardiogram, if indicated. Mammary tumors and regional lymph nodes were measured directly with calipers or by ultrasonographic imaging.

Histology

Histologic evaluation was performed according to the World Health Organization classification scheme.[24] In cases of multiple mammary masses, the most malignant tumor was considered the basis for further patient management. The presence of progesterone and estrogen receptors was examined in a subset of cases by immunohistochemical methods.[25,26]

Postoperative Treatment Groups

The control group (group I) consisted of dogs whose owners did not wish to pursue adjuvant treatment. Dogs whose owners elected adjuvant treatment were randomized to 1 of 2 treatment groups (group II and III).

Group II received 5 doses of doxorubicin[a] at a dosage of 30 mg/m² given as 20–30-minute IV infusions 3 weeks apart. These patients were pretreated with dexamethasone[b] at a dosage of 0.1 mg/kg IV. Group III received 5 doses of docetaxel[c] at a dosage of 30 mg/m² given as 30-minute IV infusions 3 weeks apart. The patients that received docetaxel were pretreated with dexamethasone at a dosage of 0.1 mg/kg IV and diphenhydramine[d] at a dosage of 1 mg/kg IV. Chemotherapy was scheduled to start 14 days after surgery. Before each chemotherapy treatment, a CBC and serum biochemistry profile were performed. Before each treatment with doxorubicin, an ECG was recorded and, if indicated by changes in the ECG or cardiac auscultation, an echocardiogram was performed. Toxicity was graded according to the Veterinary Cooperative Oncology Group–Common Terminology Criteria for Adverse Events v1.0.[27]

Follow-Up Examinations

Follow-up examinations were scheduled at 6 weeks and 3, 6, 9, 12, 18, 24, and 48 months after completion of chemotherapy in groups II and III. Dogs in the control group were scheduled for re-examination at the same time points after surgery. Follow-up examination included physical examination, CBC, serum biochemistry profile, and thoracic radiographs. If indicated by abnormalities on physical examination, blood work or radiographs, an abdominal ultrasound, an ECG, and an echocardiogram were performed. Local recurrence was defined as a recurrent mass at the surgery site with confirmation by cytology or histology in cases in which owners gave their consent. In cases in which cytologic or histologic confirmation was not possible, any mass developing at the surgery site was considered a recurrence. Cytologic examination, histologic examination, or both of metastatic lesions was performed if possible. Postmortem examination was performed in cases in which owners gave their consent.

Statistical Analysis

Endpoints that were evaluated included local recurrence, distant metastasis, and overall survival. The recurrence-free interval was defined as the time from surgery to tumor recurrence in the surgical field. The metastasis-free interval was defined as the time from surgery to the detection of distant metastasis as documented on thoracic radiographs, abdominal ultrasound, or both. Overall survival was defined as time from surgery to death from any cause.

Kaplan-Meier product limit analysis was used for recurrence-free interval, metastasis-free interval, and overall survival analyses. Dogs were censored if their tumor had not recurred (recurrence-free interval analysis) or no distant metastases had been detected (metastasis-free interval analysis) at time of death or data accrual closure.

In the survival analysis, dogs were censored if they were alive at the time of data accrual closure. In those dogs in which postmortem examination was not performed, determination of whether the cause of death was tumor-related was not possible with certainty. Therefore, dogs that died or were euthanized were not censored even if cause of death was seemingly not tumor-related. Cox forward regression analysis was used to evaluate the following variables for their influence on recurrence-free interval, metastasis-free interval, and overall survival: sex (neutering status), body weight, age, clinical stage, histologic stage, number of tumors, tumor size (longest dimension), tumor fixation to underlying structures, ulceration, regional lymph node status, progesterone and estrogen receptor status, type of surgery, and treatment type. The influence of these variables on whether each dog developed a local recurrence was analyzed by multivariate logistic regression analysis.

To verify the comparability of the treatment groups, comparisons with regard to age, weight, sex, number of tumors, tumor size, type of surgery, clinical stage, and histologic stage were performed by a Kruskal-Wallis test for continuous variables and Fisher's exact test for categorical variables.

$P < .05$ was considered significant. All statistical analyses were performed with SPSS software.[e]

Results

Patient Characteristics

Thity-one dogs fulfilled the entry criteria between April 1998 and March 2000. Of these, 19 dogs entered the control group (group I). The remaining 12 dogs received postoperative chemotherapy. Six dogs were randomized to receive doxorubicin (Group II) and 6 to

Table 1. Distribution of age, body weight, sex, type of surgery, number of tumors, tumor size (longest dimension), clinical stage, and histologic stage of dogs with malignant mammary tumors within the treatment groups as well as the comparison of the 3 groups with regard to these parameters. Group I: control group, group II: adjuvant treatment with doxorubicin, group III: adjuvant treatment with docetaxel.

Group	n	Median Age (Range)	Median Body Weight (Range)	Gender f/fs	Type of Surgery Radical/Partial Mastectomy	Number of Tumors	Median Tumor size* (Range)	Clinical Stage	Histologic Stage
I	19	11 years (7–14 years)	21 kg (4–45 kg)	15/4	9/10	1–9	64 mm (14–98 mm)	I: 2 II: 5 III: 9 IV: 3	II: 16 III: 3
II	6	11 years (5–14 years)	29 kg (22–65 kg)	4/2	3/3	1–9	36 mm (30–115 mm)	II: 1 III: 3 IV: 2	II: 4 III: 2
III	6	13 years (7–14 years)	10 kg (6.5–12.5 kg)	4/2	2/4	1–5	66 mm (25–75 mm)	II: 2 III: 4	II: 6
P Value		.51	.029	.61	.89	.12	.91	.87	.34

f, female; fs, spayed female.
* Longest dimension.

receive docetaxel (Group III). The study dogs belonged to 16 breeds. Breeds represented by more than 2 individuals were: mixed-breed (n = 10), Dachshund (n = 5), Terrier (n = 3), and Cocker Spaniel (n = 3). The remaining 10 dogs belonged to the following breeds: German Shepherd, German Pointer, Afghan, Boxer, Labrador Retriever, Golden Retriever, Leonberger, Poodle, Rottweiler, and Schnauzer. The median age was 12 years (range, 5–14 years); the median body weight was 21 kg (range, 4–65 kg). Eight dogs were spayed. Three dogs had been spayed between the ages of 3 and 10 years. For 5 dogs, information on the age at time of ovariohysterectomy was not available. The distribution of patients' age, body weight, and sex within the groups is shown in Table 1. Radical mastectomy was performed in 16 dogs, and 17 underwent partial mastectomy. None of the dogs was ovariohysterectomized at the time of surgery. The median follow-up period was 258 days (range, 13–2,585 days).

Tumor Characteristics

The median number of tumors in the mammary chains per dog was 3 (range, 1–9), and the median tumor size at the longest dimension was 66 mm (range, 14–115 mm). Sixteen tumors were simple carcinomas, 2 of which were anaplastic, and 12 tumors were complex carcinomas. In addition, there was 1 squamous cell carcinoma and 2 carcinomas with benign mesenchymal components. The tumors of 26 dogs were evaluated as histologic stage II. Five dogs had stage III mammary neoplasia. The distribution of tumor number, size, clinical stage, and histologic stage within the groups is shown in Table 1. In 15 cases, estrogen and progesterone receptors were examined; 5 dogs were estrogen-positive and 6 were progesterone-positive.

Local Control

Eleven dogs developed local recurrence. Time to recurrence ranged from 13 to 2,585 days (median not reached). Multivariate logistic regression revealed that none of the analyzed variables influenced the likelihood of the development of local recurrence. Dogs with no postoperative treatment developed local recurrence in 8 instances and had a median recurrence-free interval of 294 days (range, 13–1,155 days; 1-, 2- and 3-year local control rates of 49%, respectively). In patients that received adjuvant chemotherapy, local recurrence was documented in 3 dogs and the median recurrence-free interval was not reached (range, 39–2,585 days; 1-, 2- and 3 year local control rates of 83% and 63%, respectively). There was no statistical difference between these 2 groups of patients ($P = .172$). Stratification by type of treatment revealed that in dogs treated with doxorubicin local control duration ranged from 39 to 2,585 days (median not reached), whereas the docetaxel group had a median recurrence-free interval of 434 days (range, 143–1643 days). No significant difference among the 3 patient groups was apparent ($P = .39$). None of the

analyzed variables had a significant influence on the duration of local control.

Distant Metastasis

Five dogs presented with distant metastasis, and another 13 dogs developed metastases during the study period. The location of the metastases was lungs (n = 18), liver (n = 5), bone (n = 4), spleen (n = 4), central nervous system (n = 3), and skin, eye, pancreas, muscle, and adrenal gland (n = 1, respectively). Seven dogs had metastases at multiple (2–8) sites. Median time to metastasis was 294 days (range, 0–2,585 days). Dogs with no postoperative treatment developed distant metastasis in 9 instances and had a median time to metastasis of 294 days (range, 0–1,155 days). In dogs that received either doxorubicin or docetaxel adjuvant chemotherapy, 4 developed distant metastasis. The median time to metastasis in these dogs was 231 days (range, 0–2,585 days). There was no statistical difference between the treated group and the nontreated group (P = .71). Stratification by type of treatment revealed that dogs treated with doxorubicin had a median time to metastasis of 231 days (range, 0–2,585 days), whereas the docetaxel group had a median metastasis-free interval of 167 days (range, 99–2,126 days). No significant difference among the 3 patient groups was found (P = .93). Multivariate Cox regression analysis of patient parameters revealed that the variables lymph node metastasis (P = .009) and tumor fixation to underlying structures (P = .043) had a significant influence on the duration of the metastasis-free interval.

To eliminate any influence of dogs with histologic stage III disease on the metastasis-free interval parameter, dogs with histologic stage II tumors were analyzed separately. In this subset of dogs (n = 26), median time to metastasis was 490 days (range, 13–2,585 days). Dogs with no postoperative treatment (n = 16) had a median time to metastasis of 490 days (range, 13–1,155 days). In the group of patients that received either doxorubicin or docetaxel adjuvant chemotherapy (n = 10), time to metastasis ranged from 99 to 2,585 days, with the median not reached. There was no statistical difference between the treated group and the nontreated group (P = .64). Stratification by type of treatment revealed that in dogs treated with doxorubicin (n = 4) the median time to metastasis ranged between 140 and 2,585 days with no median reached, whereas the docetaxel group (n = 6) had a median metastasis-free interval of 167 days (range, 99–2,126 days). Again, no significant difference among the 3 patient groups was apparent (P = .62). Univariate Cox regression analysis revealed that patient age (P = .023) and tumor fixation to underlying structures (P = .014) had significant influence on the duration of the metastasis-free interval. On multivariate analysis however, only age remained significant (P = .017).

Overall Survival

At the time of data accrual closure, 2 dogs were still alive and the remaining 29 dogs had died. The overall
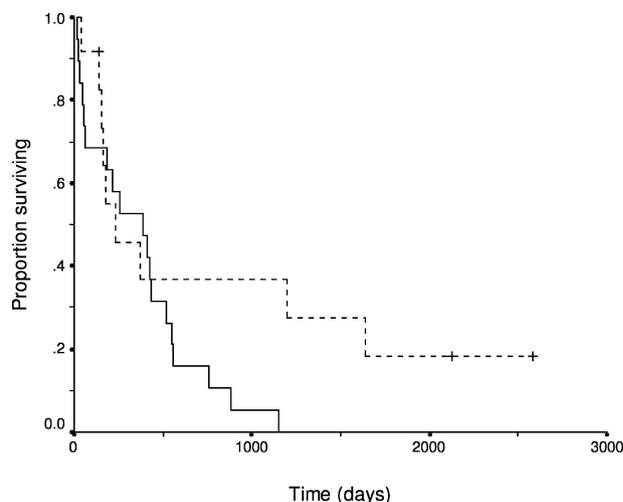

Fig 1. Kaplan-Meier curve depicting the survival time of dogs with invasive malignant mammary tumors (n = 31). The dotted line represents dogs that received postoperative chemotherapy with doxorubicin or docetaxel (n = 12; median survival time 231 days, range 39–2,585 days; 1-, 2–3-, 4-, 5–7-year survival rates 45.8%, 36.7%, 27.5%, and 18%, respectively) and the continuous line represents dogs that did not receive adjuvant treatment (n = 19; 390 days, range 13–1,155 days; 1-, 2-, 3-year survival rates 52.6%, 15.8%, and 5.3%, respectively, P = .12). (Vertical bars represent dogs censored at analysis.)

median survival time was 370 days (range, 13–2,585 days). Dogs with no postoperative treatment had a median survival time of 390 days (range, 13–1,155 days; 1-, 2-, 3-year survival rates of 52.6%, 15.8%, and 5.3%, respectively). The cause of death in this group was metastatic disease in 12 dogs, tumor recurrence in 4 dogs, and non–tumor-related causes in 3 dogs. The group of patients that received either doxorubicin or docetaxel adjuvant chemotherapy had a median survival time of 231 days (range, 39–2,585 days; 1-, 2–3-, 4-, 5–7-year survival rates of 45.8%, 36.7%, 27.5%, and 18%, respectively). Two dogs in the treatment group were alive at the time of data accrual closure at 1,876 and 2,335 days. The cause of death in the remaining dogs was metastatic disease in 6 dogs, tumor recurrence in 2 dogs, and non–tumor-related causes in 2 dogs. No statistical difference in overall survival duration was found between the treated group and the nontreated group (P = .12, Fig 1).

Stratification by type of treatment revealed that dogs treated with doxorubicin had a median survival time of 231 days (range, 39–2,585 days), whereas the docetaxel group had a median metastasis-free interval of 181 days (range, 143–2,126 days). No significant difference among the 3 treatment groups was shown (P = .29). Multivariate Cox regression analysis showed that patient age (P = .018) and histologic stage (P < .001) had a significant influence on survival time (Fig 2).

Treatment Toxicity

Treatment with doxorubicin led to toxicosis in 3 dogs: grade 1 diarrhea in 1 dog after the first treatment and grade 1–2 vomiting and diarrhea in a second dog after
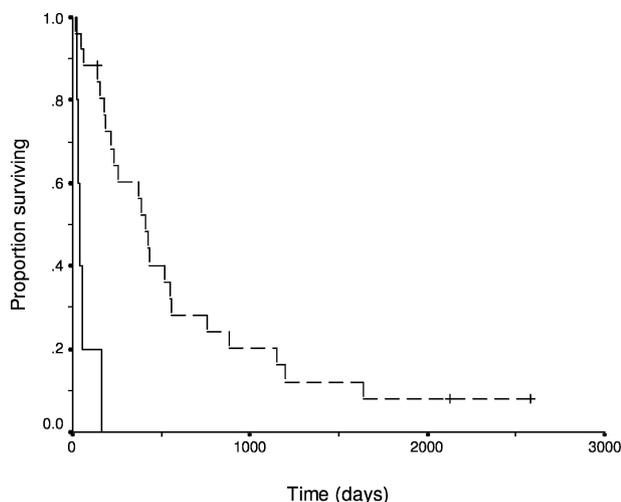
Fig 2. Kaplan-Meier curve depicting the local control duration of dogs with invasive malignant mammary tumors (n = 31). The dotted line represents dogs with histologic stage II disease (n = 26, median 406 days), and the continuous line represents dogs with histologic stage III disease (n = 5, median 39 days, $P < .001$). (Vertical bars represent dogs censored at analysis.)

the 4th, 5th, and 6th treatments. Slight alopecia (grade 1) and cutaneous hyperpigmentation (grade 1) were seen in another dog (West Highland-White Terrier mix). One dog exhibited a low-normal neutrophil count ($3.3 \times 10^3/ \mu L$) but otherwise no myelosupresion was noted.

Similarly, no signs of myelosuppression were observed in the CBCs of the dogs treated with docetaxel. The total number of dogs that experienced toxicosis after docetaxel was 4. One dog developed grade 1 diarrhea responsive to dietary management after each treatment. A second dog had grade 2 vomiting after the first treatment but showed no signs of gastrointestinal toxicity after additional doses. The most common signs of drug toxicity in the dogs treated with docetaxel were cutaneous allergic reactions. Pruritus (grade 1) and erythema of the skin (grade 1) in the inguinal and ventral area occurred during each treatment in 1 dog. A second dog experienced grade 2 pruritus also during each administration of docetaxel. Two dogs displayed mild signs of uneasiness during treatments without clinically detectable signs of pruritus or cutaneous erythema. The observed dermatologic changes began during the first 5 minutes of the IV infusion of docetaxel and abated approximately 10 minutes after the end of each drug administration. Two patients displayed no signs of toxicity during or after the treatment with docetaxel.

Discussion

The aim of this study was to evaluate the efficacy of adjuvant, postoperative chemotherapy with doxorubicin or docetaxel in dogs with highly invasive malignant mammary tumors in comparison to surgery alone. Statistical evaluation showed that the dogs treated with adjuvant chemotherapy after surgery did not experience any significant benefit in duration of the recurrence-free interval, time to metastasis, or overall survival in

comparison to dogs with only surgical intervention. This finding is in contrast to a recent study in which postoperative chemotherapy with cyclophosphamide and 5-fluoruracil was revealed to improve survival and disease-free interval.[12] In that study encompassing 16 patients, dogs were censored if they had died of apparently non–tumor-related causes, whereas in this study patients were only censored if alive at the time of data accrual closure. Additionally, in the previous investigation, multivariate analysis to identify the possible influence of variables other than treatment on patient outcome was not available. In this study, the median recurrence-free interval, time to metastasis, and survival of the untreated control group (including even histologic stage III dogs) amounted to 294 and 490 days. In the cited study, the control group exhibited a comparably short median disease-free interval of 2 months and a median survival of 6 months.[12] Comparisons between different studies is difficult, nonetheless the comparably poor outcome of the untreated dogs in the previous study may have contributed to the statistical difference detected. This difference could not be corroborated in the present study in which the control group exhibited a more favorable treatment outcome. In both studies, owners' decisions and not a randomization scheme was the basis for patients being allocated to the control or treatment group. This may account for bias because many factors such as presentation or perception of prognosis affect the owners' choice whether to pursue treatment, often resulting in negative bias in cases with adjuvant treatment. This instance may be reflected by less favorable treatment outcome of the treatment groups.

The low number of patients in the present study is one of its main limitations. Considering the diversity of canine mammary tumors as an entity, low patient numbers bear the risk of not including a representative population and decrease the ability of a study to detect significant differences that may be present. The present investigation had very specific inclusion criteria, accruing only patients with malignant tumors of histologic stages II and III with the goal of studying a more homogenous population with respect to the biologic behavior of the tumor, possibly enabling the detection of differences in outcome with smaller populations. These strict entry criteria also may serve as an explanation why patient numbers were low, because these conditions were only fulfilled in a small subset of dogs. Therefore, it may be possible that adjuvant treatment with doxorubicin or docetaxel is of benefit in invasive mammary carcinoma, but patient numbers were too low to detect a statistical difference among the treatment groups. The observed tendency for the subset of dogs treated with adjuvant doxorubicin or docetaxel to experience higher long-term survival and local control rates suggests very cautious support for this conclusion. To what extent a higher number of patients may lead to the detection of statistical differences among treatment groups must, however, be verified in future studies. Also, in the present population of dogs, the patients that received adjuvant doxorubicin showed a tendency toward an

improved outcome compared to docetaxel. Again, to what extent this is attributable to population bias or to a true superior efficacy of doxorubicin remains to be clarified with larger study populations. An additional limiting factor that needs mentioning is the median follow-up time of 258 days, which may have an impact on the results of the study because patients with recurrence or metastasis later in the course of their disease would be missed in the outcome analysis.

Several prognostic factors have been described for canine mammary tumors, including patient age, tumor size, clinical stage, histologic type, stage and grade, and estrogen status, as well as ovariohysterectomy status and time.[8,28,29] A number of variables were tested for prognostic influence in the present population of dogs. Although none of the analyzed parameters proved influential on the duration of local control, lymph node metastasis as well as tumor fixation to underlying structures had a significant influence on the metastasis-free interval, both factors reflecting the aggressive nature of the tumor. In the evaluation of factors affecting the duration of overall survival, only age and histologic stage had significant influence. This finding again is in agreement with other studies in dogs.[8,9,28,30] The variable age may not reflect only tumor-related influences,[3] therefore, histologic stage may be regarded as the most influential tumor-associated variable affecting survival duration in this study. Other strong prognostic factors such as tumor size and clinical stage proved not to be significant in this population. This finding may be associated with the high-risk nature of the selected cases, for which these parameters may lose their impact on treatment outcome.

A second goal of the present study was to document tolerance and toxicity of docetaxel in dogs with cancer. To the authors' knowledge, this is the first description of the use of docetaxel in clinical canine cancer patients. The dosage used was derived from preclinical studies with Beagle dogs.[17] In the 6 dogs treated with this second generation taxane, overall toxicity was considered mild. The experimental studies in Beagles described hematologic and gastrointestinal toxicosis.[17,31] Hematologic toxicosis was not observed in the dogs in the present study. Sequential CBCs at regular intervals between treatments were not performed however, and consequently, transient decreases in neutrophil numbers may have gone undetected. Adverse gastrointestinal effects have been revealed to be dose-limiting in dogs, with moderate vomiting and diarrhea observed.[17,31] Gastrointestinal toxicosis was mild and well tolerated in the present study. Allergic skin reactions were the most frequently encountered adverse effects in the present study. These can be attributed to the solvent polysorbate 80, which is capable of inducing histamine release in dogs and likely are not because of the drug itself.[17,32] In the experimental setting, allergic reactions included marked clinical and cardiovascular signs such as generalized erythema, facial swelling, hypotension, and tachycardia.[17,32] The allergic reactions seen in the dogs of the present study were mild, localized, and transient. Generalized erythematous or edematous reactions and

marked cardiovascular signs were not observed. This result may be ascribed to pretreatment with dexamethasone and diphenhydramine, allowing for more tolerable adverse effects with the use of docetaxel.

Footnotes

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Appendix

Clinical staging of canine malignant mammary tumors based on World Health Organization TNM classification of tumors in domestic animals.[23]

Tumor	Regional Lymph Node	Distant Metastasis
T0: no measurable tumor	N0: no Ln. metastasis	M0: no distant metastasis
T1: <3 cm	N1: Ln. metastasis	M1: distant metastasis
T2: 3–5 cm		
T3: >5 cm		
T4: inflammatory carcinoma		
a: not fixed	a: not fixed	
b: fixed	b: fixed	

Clinical stage	Tumor	Regional Lymph Node	Metastasis
I	T1	N0	M0
II	T0, T1	N1	M0
	T2	N0, N1	M0
III	T3	N0, N1	M0
	T0–T3	N1	M0
IV	T0–T3	N0, N1	M1
V	T4	N0, N1	M1

Histologic staging system of canine malignant mammary gland tumors.[8]

Stage

0	Tumor cells limited to ductal tissue
I	Tumor cells invading into stromal tissue
II	Vascular/lymphatic invasion, regional lymph node metastasis
III	Distant metastasis present