Journal of Feline Medicine and Surgery (2008) **10**, 324–331
doi:10.1016/j.jfms.2007.12.009

ELSEVIER

jfms

A comparison of toxicity of two dosing schemes for doxorubicin in the cat

Rachel A Reiman DVM*, Glenna E Mauldin DVM, MS, Dipl ACVIM (Oncology), ACVN[a], Guy Neal Mauldin DVM, Dipl ACVIM (Internal Medicine and Oncology), ACVR (Radiation Oncology)[a]

Cancer Treatment Unit, Department of Veterinary Clinical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA 70803, United States

Doxorubicin is a commonly used and effective treatment for a variety of tumors in both people and cats. However, the use of this drug in cats has been associated with side effects such as renal injury, myelosuppression, anorexia, and weight loss. The goal of this study was to compare the toxicities associated with two dosing schemes for doxorubicin in tumor-bearing cats. Group A cats received 1 mg/kg of doxorubicin, while group B cats received 25 mg/m^2 of doxorubicin plus 22 ml lactated Ringer's solution per kilogram body weight subcutaneously. Toxicities were evaluated using laboratory data, physical examination, and history, and were graded using a standardized scale and compared between groups. Post-treatment neutrophil counts were significantly lower among cats in group B compared to cats in group A ($P \leq 0.001$), although complete blood counts were not evaluated at identical intervals in all cases. No other significant differences in the type, frequency or severity of clinical or laboratory toxicities were noted between groups, and no episodes of sepsis were recognized in either group. The results of this study suggest that higher doses of doxorubicin may not be associated with an increased risk of toxicity in the cat. Additional studies are still indicated to determine optimal dosing for doxorubicin in this species.

Date accepted: 23 December 2007

The anthracycline antibiotic doxorubicin (Adriamycin; Adria Labs) is a widely used and highly effective chemotherapeutic agent in both people and animals. Doxorubicin and a similar compound, daunorubicin, were originally isolated from *Streptomyces* species; second generation agents such as idarubicin and epirubicin are synthetically derived (Doroshow 2001). Anthracycline antibiotics inhibit topoisomerase II, a nuclear enzyme needed to access and segregate portions of DNA required for cellular functions. When topoisomerase II is inhibited, these segments of DNA cannot be accessed for transcription, leading to double-stranded DNA breaks and cell death (Sui and Moore 2005). Doxorubicin causes additional cytotoxicity through oxidative damage to proteins and membranes of neoplastic cells by oxygen free radical formation. At high concentrations doxorubicin also intercalates between base pairs of DNA, thereby inhibiting DNA polymerase. However, this effect is of questionable clinical relevance because the drug doses required for significant intercalation to occur are associated with unacceptable side effects in vivo (Sui and Moore 2005).

Elimination of doxorubicin is primarily through the bile, with less than 10% excreted in the urine. Enterohepatic recirculation does not occur (Doroshow 2001). Cardiotoxicity is dose limiting in people and dogs, although other potential toxicities include myelosuppression, alopecia, vomiting, and diarrhea. Renal toxicity has been documented in rats, rabbits, cats, and rarely in people (Fajardo et al 1980, Bertani et al 1982, Cotter et al 1984).

Reports describing the use of doxorubicin in cats first appeared in the late 1970s (Henness et al 1977). Since that time, efficacy has been documented against a variety of feline tumors,

*Corresponding author. Current address: Animal Emergency Center, 2100 W Silver Spring Dr, Glendale, WI 53209, United States. Tel: +1-414-540-6710; Fax: +1-414-540-6720. E-mail: aecrachel@aol.com
[a]Current address: Western Veterinary Specialist Centre, 1802 – 10th Avenue SW, Calgary, Alberta, Canada T3C 0J8.

1098-612X/08/040324+08 $34.00/0

including lymphoma and vaccine site sarcomas (Jeglum et al 1985, Mauldin et al 1988, Barber et al 2000). However, studies published between 1984 and 1993 suggested that use of the drug in cats could be associated with significant toxicity, including renal injury, myelosuppression, anorexia, and weight loss (Cotter et al 1984, O'Keefe and Schaeffer 1992, O'Keefe et al 1993). Based in part on these reports, veterinary oncologists are often conservative when dosing doxorubicin in cats. While cats in many early reports were given individual doses of doxorubicin similar to those still used in dogs (30–40 mg/m^2) and cumulative doses of up to 300 mg/m^2, the typically reported individual dose is now 1 mg/kg or approximately 20 mg/m^2. Unfortunately, decreased dose intensity is a well established cause of compromised drug efficacy (Chu and DeVita 2001). In fact, some studies in cats document decreased efficacy for doxorubicin in tumors that might otherwise be expected to respond, based on experience in other species (Zwahlen et al 1998). This retrospective study was, therefore, initiated to investigate the toxicities associated with an approximately 25% increased dose of doxorubicin (25 mg/m^2) given with subcutaneous fluids in tumor-bearing cats, and to compare these to the toxicities observed after a more traditional dose (1 mg/kg or roughly 20 mg/m^2). If observed toxicities do not differ between these two regimes, then routine administration of a higher doxorubicin dose in cats with a variety of malignancies should be reasonable and may result in improved responses to therapy.

Materials and methods

Medical records of all cats receiving doxorubicin at the Louisiana State University Cancer Treatment Unit between 1998 and 2004 were reviewed. Data collected from the medical records included signalment; tumor type; age at first doxorubicin administration; total cumulative dose of doxorubicin administered; concurrent chemotherapy administered; hematology, serum biochemistry, and urinalysis results; and the incidence and severity of side effects. Follow-up time was measured from the date of initiation of chemotherapy to the date of death because of tumor or complications caused by tumor treatment, the date of death from other causes, or the date of last recorded contact if the animal was lost to follow-up. Cats were divided into one of two groups based on dose of doxorubicin administered: all cats receiving doxorubicin between 1998 and 2003 were treated at 1 mg/kg, and were placed in group A; all cats receiving doxorubicin between 2003 and 2004 were treated at 25 mg/m^2 and also received subcutaneous fluids, and were placed in group B.

Drug administration protocol

All cats underwent baseline evaluation of renal function. Pretreatment electrocardiograms and reassessment of renal function were performed immediately prior to each administration of doxorubicin at the discretion of the attending clinician. Doxorubicin was diluted to a concentration of 1 mg/ml with 0.9% saline according to manufacturer's instructions. All cats were pretreated with 0.2 mg dexamethasone (Azium; Schering Plough) intravenously immediately prior to doxorubicin administration to prevent anaphylactic reactions. Doxorubicin was given intravenously over 5–10 min through a perfectly placed intravenous catheter either in a medial saphenous or cephalic vein. All cats treated at 25 mg/m^2 of doxorubicin (group B cats) were also given 22 ml lactated Ringer's solution per kilogram body weight subcutaneously immediately after each treatment.

Assessment of toxicity

Toxicity was evaluated by monitoring laboratory data, physical examination parameters, and information obtained from the owners. Toxicities were graded according to a previously published modification of the Eastern Cooperative Oncology Group toxicity criteria (Table 1) (Rassnick et al 2000).

Statistical analysis

Continuous parameters were assessed for normality using a Kolmogorov–Smirnov test, and then compared between group A and group B cats using a *t* test for normally distributed data, and a Mann–Whitney test for non-parametric data. For continuous parameters measured over time (such as neutrophil count and blood urea nitrogen), data were first tested for normality using a Kolmogorov–Smirnov test. If the data were normally distributed, a repeated measure analysis of variance (ANOVA) was performed; if they were not, the data were log transformed and a repeated measure ANOVA was then performed. Categorical data were compared between groups using a χ^2 analysis. Type I error was maintained at 0.05 for all comparisons.

Table 1. Criteria for toxic effects in cats receiving doxorubicin (Rassnick et al 2000)

Toxicity and grade	Criteria
Neutropenia	
0	None
1	1500−3000 neutrophils/μl
2	1000−1500 neutrophils/μl
3	500−1000 neutrophils/μl
4	<500 neutrophils/μl
Renal	
0	None
1	Creatinine 1.5−3 mg/dl
2	Creatinine 3−4 mg/dl
3	Creatinine 4−5 mg/dl
4	Creatinine >5 mg/dl
Anorexia	
0	None
1	Inappetence
2	Anorexia < 3 days duration
3	Anorexia > 3 days but <5 days duration
4	Anorexia > 5 days duration; 10% weight loss
Vomiting	
0	None
1	Nausea
2	Sporadic, self-limiting
3	1/5 Episodes per day, <2 days
4	6−10 Episodes per day, requires hospitalization
Diarrhea	
0	None
1	Soft stools, responds to dietary modification
2	1−4 Watery stools per day, <2 days
3	4−7 Watery stools per day, or >2 days
4	>7 Watery stools per day or bloody, requires hospitalization

Results

One hundred and eighty-seven doses of doxorubicin were given in 60 cats with spontaneously occurring neoplasia. Eighteen of the 40 cats in group A had lymphoma (45%), nine had mammary gland adenocarcinoma (22.5%), six had vaccine associated sarcomas (15%), two had anaplastic sarcomas (5%), and there was one each of intestinal adenocarcinoma, apocrine gland adenocarcinoma, ceruminous gland adenocarcinoma, basal cell carcinoma and mesothelioma. Eight of the 20 cats in group B had lymphoma (40%), four had vaccine associated sarcomas (20%), two had intestinal adenocarcinoma (10%), two had salivary gland adenocarcinoma (10%), and there was one each of mammary gland adenocarcinoma, pulmonary carcinoma, bronchoalveolar carcinoma and oral squamous cell carcinoma. There was no difference in the distribution of tumor types treated in group A versus group B ($P = 0.20$). Median age at first administration of doxorubicin was 10.5 years (range 3−18 years) in group A cats and 11.5 years (range 1−17 years) in group B cats. There was no difference in age at first dose of doxorubicin between the two groups ($P = 0.82$). Median overall follow-up in all 60 cats was 120 days (range 0−1163 days).

One hundred and twenty-nine doses of doxorubicin were given at 1 mg/kg in 40 cats (group A). Fifty-eight doses were given at 25 mg/m^2 with subcutaneous fluids in 20 cats (group B). A median of 3 doses was given to all cats (range 1−6): cats in group A received a median of 3 doses (range 1−6) and cats in group B received a median of 2.5 doses (range 1−6). Median cumulative dose was 53.5 mg/m^2 (range 14.7−121.3 mg/m^2) in group A cats and 61.3 mg/m^2 (range 23.2−144.8 mg/m^2) in group B cats. There was no difference in either number of doses of doxorubicin received ($P = 0.45$), or in the total cumulative dose of doxorubicin received ($P = 0.49$), when cats in group A were compared to cats in group B. Twenty cats in group A were given doxorubicin alone and 20 were given doxorubicin in sequential combination with other chemotherapeutics. Seven cats in group B were given doxorubicin alone, and 13 cats were given doxorubicin in sequential combination. Other agents used included vincristine, cyclophosphamide, L-asparginase, carboplatin, and cytarabine. No cats in either group received doxorubicin concurrently with any other chemotherapy drug. There was no difference between the two groups in the proportion of cats that received doxorubicin as a single agent, versus as part of a sequential combination protocol ($P \leq 1.0$).

Toxicity

Gastrointestinal toxicity was the most commonly reported side effect in both groups of cats. Vomiting and anorexia were the most common complaints. Overall, vomiting was reported after 36 of 187 doses of doxorubicin (19.2%). Group A cats had 24 episodes of vomiting in 129 doses (18.6%) of doxorubicin while group B cats had

12 episodes of vomiting in 58 doses (20.6%) of doxorubicin. There were 11 (8.5%) episodes of grade I vomiting, 12 (9.3%) episodes of grade II vomiting, and one (0.8%) episode of grade III vomiting in 129 doses given to group A cats. There were four (7%) incidents of grade I, eight (14%) incidents of grade II, and no incidents of grade III vomiting after 58 doses of doxorubicin in group B cats. Grade IV vomiting did not occur in either group of cats. There was no difference between group A and group B in the overall number of episodes of vomiting ($P \leq 1.0$), or in the distribution of cats with vomiting among grades I–IV ($P \leq 1.0$).

Anorexia occurred a total of 20 times (11.6%) after administration of 187 doses of doxorubicin in all cats. Group A cats had 14 episodes (10.9%) in 129 doses of doxorubicin while group B cats had six episodes (10.3%) in 58 doses of doxorubicin. Twelve episodes (9.3%) of grade I anorexia and two episodes (1.6%) of grade II anorexia occurred in group A cats. Four episodes (6.9%) of grade I and two episodes (3.4%) of grade II anorexia were reported in group B cats. No episodes of grade III or IV anorexia were reported in either group of cats. There was no difference between groups in the overall number of episodes of anorexia ($P \leq 1.0$) or in the distribution of cats with anorexia among grades I–IV ($P \leq 1.0$).

The median pretreatment neutrophil count was $8.45 \times 10^3/\mu l$ (range $2.0–64.9 \times 10^3/\mu l$) in group A cats and $7.0 \times 10^3/\mu l$ (range $0.2–18.9 \times 10^3/\mu l$) in group B cats. There was no difference between treatment groups in pretreatment neutrophil count ($P = 0.17$). Complete blood counts (CBCs) were performed at intervals based primarily on treatment schedule, which varied with protocol. Median overall time to follow-up CBC was 21 days (range 2–49 days) post-treatment with a median of 21 days in group A cats (range 2–49 days) and a median of 20.5 days in group B cats (range 5–35 days). The median post-treatment neutrophil count was $8.6 \times 10^3/\mu l$ (range $2.1–116.4 \times 10^3/\mu l$; $n = 83$) in group A cats and $5.55 \times 10^3/\mu l$ (range $0.3–52.4 \times 10^3/\mu l$; $n = 38$) in group B cats. Although cats in both treatment groups had median post-treatment neutrophil counts that were well within the established normal laboratory range of $2.5–12.5 \times 10^3/\mu l$, post-treatment counts were significantly lower among cats in group B compared to cats in group A ($P \leq 0.001$). Median neutrophil counts with ranges are presented by week post-doxorubicin therapy for both groups in Table 2. The greatest difference in median count occurred in week 3 post-treatment, days 15–21 (see Table 2). However, there was no significant change in neutrophil count over time among cats in either group ($P = 0.79$ for group A; $P = 0.23$ for group B).

There were more episodes of neutropenia among cats in group B than among cats in group A ($P \leq 0.001$), but one incident of grade I neutropenia and two incidents of grade III neutropenia occurred in a single cat in group B. This was a feline leukemia virus positive cat with stage V lymphoma that was neutropenic upon initial presentation. Overall, there were no incidents of grade I neutropenia, one incidence of grade II neutropenia (0.8%), and no incidents of grade III or IV neutropenia in the 129 doses of doxorubicin given in group A cats. There were two incidents of grade I (3.4%) neutropenia, two

Table 2. Median neutrophil counts by week post-doxorubicin therapy

	Week 1 (day 0–7)	Week 2 (day 8–14)	Week 3 (day 15–21)	Week 4 (day 22–28)
Group A				
Median neutrophils ($\times 10^3/\mu l$)	9.3	7.4	9.8	10.0
Range	3.2–56.3	3.0–37.2	3.0–35.9	7.0–16.9
Observations	$n = 11$	$n = 28$	$n = 64$	$n = 6$
Neutropenic episodes	Grade II (1)			
Group B				
Median neutrophils ($\times 10^3/\mu l$)	8.8	5.8	5.1	8.6
Range	0.3–10.2	0.8–33.9	1.3–37.7	4.6–35.2
Observations	$n = 10$	$n = 12$	$n = 22$	$n = 5$
Neutropenic episodes	Grade III (1), grade IV (1)	Grade II (2), grade III (1)	Grade I (2)	

incidents of grade II (3.4%) neutropenia, two incidents of grade III (5.1%) neutropenia, and one incident of grade IV neutropenia in the 58 doses of doxorubicin given in group B cats. There was no difference between groups in the distribution of doses associated with neutropenia among grades I–IV ($P \leq 1.0$).

The median pretreatment blood urea nitrogen (BUN) was 26 mg/dl (range 15–68 mg/dl) in group A cats and 24.5 mg/dl (range 12–38 mg/dl) in group B cats. The median pretreatment serum creatinine concentration was 1.55 mg/dl (range 0.7–3.1 mg/dl) in group A cats and 1.25 mg/dl (0.8–2.8 mg/dl) in group B cats. While there was no difference in pretreatment BUN between groups ($P = 0.21$), pretreatment serum creatinine concentration was higher in group A cats compared to cats in group B ($P = 0.005$). Renal values were evaluated prior to subsequent doses of doxorubicin at the discretion of the attending clinician. The median post-treatment BUN was 27 mg/dl (range 17–120 mg/dl; $n = 20$) in group A cats and 22 mg/dl (range 16–60 mg/dl; $n = 36$) in group B cats. The median post-treatment serum creatinine concentration was 1.75 mg/dl (range 0.9–4.3 mg/dl; $n = 20$) in group A cats and 1.4 mg/dl (range 0.7–3.6 mg/dl; $n = 36$) in group B cats. There was no difference between groups with regard to BUN ($P = 0.21$) or serum creatinine ($P = 0.64$), and there was also no significant change in BUN over time among cats in either group ($P = 0.41$ for group A; $P = 0.13$ for group B). Overall 10 cats ($10/60 = 16.7\%$) became azotemic during or after treatment with doxorubicin: seven of the cats were in group A ($7/40 = 17.5\%$) and three were in group B ($3/20 = 15\%$). There was no difference between groups in the proportion of cats becoming azotemic ($P \leq 1.0$). Five group A cats ($5/40 = 12.5\%$) developed grade I azotemia and two group A cats ($2/40 = 5\%$) developed grade III azotemia. No group A cats developed grade II or IV azotemia. Two group B cats ($2/20 = 10\%$) developed grade I azotemia and one group B cat ($1/20 = 5\%$) had grade II azotemia. Grades III and IV azotemia were not observed in group B cats. There was no difference in the distribution of cats with azotemia among grades I–IV ($P \leq 1.0$).

There was no difference between groups in weight change or loss ($P = 0.27$). Clinical disease consistent with doxorubicin cardiomyopathy was not observed. One cat developed nonspecific cardiomyopathy considered to be unrelated to doxorubicin treatment 106 days after completion of chemotherapy.

Discussion

The potential complications associated with doxorubicin therapy have been investigated in both normal and tumor-bearing cats. Henness et al (1977) first described the response of normal cats to doxorubicin. Cats in this study received individual doxorubicin doses of 10–40 mg/m^2, with cumulative doses ranging from 40 mg/m^2 to 60 mg/m^2. Transient neutropenia was noted at all dose levels, most commonly at day 6, with a return to normal by day 13–245. Alopecia and slow re-growth of hair were seen in all cats, regardless of dose level. Necropsy examination of these animals revealed no gross or histopathologic lesions in any tissues.

In 1985, Cotter and colleagues documented the development of renal abnormalities in five tumor-bearing cats treated with doxorubicin. These cats were treated at doses of 30 mg/m^2 (four cats) or 40 mg/m^2 (one cat) every 21 days; total cumulative doses ranged from 130 mg/m^2 to 320 mg/m^2. The cats were followed until death, which occurred at a range of 4–7 months from initiation of treatment. The cause of death in four cats was progressive kidney disease. The cause of death in the fifth cat was metastatic mammary adenocarcinoma; this cat did not have documented azotemia, but was included in the report because of proteinuria. Four of the five cats had necropsies performed and all of these had renal lesions consistent with doxorubicin toxicity. The hearts of three cats also had lesions histopathologically similar to those seen in other species with doxorubicin toxicity.

O'Keefe and colleagues published two reports describing the hematologic and systemic toxicities of higher doses of doxorubicin in normal cats (O'Keefe and Schaeffer 1992, O'Keefe et al 1993). These cats were treated at 30 mg/m^2 every 21 days to cumulative doses of 300 mg/m^2. The most common side effects observed were anorexia and weight loss, both of which increased in severity as higher cumulative doses were given. BUN and serum creatinine concentration remained normal in three of six cats, and was increased in three of six cats. Creatinine clearance was significantly decreased in all cats. Clinical signs of heart disease were not observed in any of the animals, but fractional shortening decreased significantly over the course of the study. At necropsy, all cats had histological lesions typical of doxorubicin-induced toxicity.

Of the potential doxorubicin-related toxicities described by these and other authors, renal

injury has arguably been of greatest concern to veterinarians treating cats with this drug. Doxorubicin-induced nephrotoxicity has been documented in rats, hamsters, rabbits, cats, and people (Yesair et al 1972, Young 1975, O'Keefe et al 1993, Javiaid et al 2001). It is characterized by weight loss, anorexia, azotemia, proteinuria, hypoproteinemia, and nephrotic syndrome. Histopathology reveals glomerular epithelial cell proliferation, loss of foot processes, thickening of glomerular basement membrane, tubular and interstitial fibrosis, and atrophy of the glomerular tuft (Fajardo et al 1980, Bertani et al 1982, Klimtova et al 2002). Even though it is difficult to prove that progressive renal dysfunction in a geriatric, tumor-bearing cat that may also have unrelated kidney disease is a direct result of doxorubicin therapy, the perceived risk of irreversible injury has lead to relatively conservative dosing of this agent in this species. While early studies described the use of 30–40 mg/m^2 individual doses, the more typical current individual dose has gradually evolved to 1 mg/kg (approximately 20 mg/m^2) (Chun et al 2007). The problem with this approach is that it results in decreased dose intensity, which is one of the primary factors that determine the efficacy of any chemotherapy agent: in animal models, a dose reduction of approximately 20% can lead to a 50% decrease in cure rate (Chu and DeVita 2001). Even though an apparently complete clinical remission may initially be achieved, dose reductions in the linear phase of the dose–response curve result in loss of ability to completely eradicate the tumor because residual tumor cells remain after therapy (Sorenmo et al 2004, Boyer and Tannock 2005). This may explain why some studies describe a relatively disappointing response to doxorubicin for feline tumors such as lymphoma (Peaston and Maddison 1999, Kristal et al 2001).

Toxicity associated with the use of doxorubicin among the cats in the present study was comparable to or even less than that observed in previous studies, and did not appear to differ dramatically between the two treatment groups. This is perhaps not surprising given that even though the higher individual doses of doxorubicin received by cats in group B increased their median cumulative dose of doxorubicin by 15% compared to cats in group A, this difference in total dose was not statistically significant. The most commonly reported side effects were vomiting and anorexia, with an overall incidence of 19.6% and 11.6%, respectively; there was no difference in the frequency or severity of either of these toxicities between the two groups. Development of mild renal azotemia that may or may not have been related to doxorubicin therapy was also observed with equal frequency and severity, and an overall incidence of 16.7%. The only significant differences in toxicity found between the two groups were a lower post-treatment neutrophil count and a higher incidence of neutropenia among cats in group B compared to the cats in group A. While it is logical to conclude that these observations are the result of the higher individual doses of doxorubicin received by group B cats, these animals did not experience unacceptable myelosuppression. The median post-treatment neutrophil count in group B cats remained well within the normal range. Furthermore, the data are likely to have been confounded by the presence of a feline leukemia virus positive cat with lymphoma and bone marrow involvement in group B. In summary, then, this study could demonstrate no clinically significant difference in the rate or severity of any toxicity between the two dose groups. This suggests that a doxorubicin dose of 25 mg/m^2 plus 22 ml of subcutaneous fluids per kilogram body weight is as safe and well tolerated as a dose of 1 mg/kg in cats with neoplastic disease. It is unknown if the subcutaneous fluids given to cats in group B actually provided a renal protective effect: further work will be needed to answer this question.

It is important to note that factors other than individual doxorubicin dose or treatment with subcutaneous fluids may have contributed to the relatively low incidence of fairly mild doxorubicin-related toxicity observed among the cats in this report, when compared to previous studies. Cats in this study received lower cumulative doses of doxorubicin when compared to cats included in many earlier reports (Cotter et al 1984, O'Keefe and Schaeffer 1992, O'Keefe et al 1993). Animals in previous studies were treated at 2–6 times the median cumulative doses given to cats in this study, and this is an obvious explanation for the higher incidence of renal disease that has been observed by other investigators. Median follow-up in the current study was only 120 days, and it is also possible that the incidence of toxicity would be increased if longer follow-up had been obtained. However, the median follow-up reported here is within the time frame during which renal failure has been observed by other authors (Cotter et al 1984, O'Keefe and Schaeffer 1992, O'Keefe et al 1993).

Finally, very few necropsies were permitted by the owners of the cats included in this study. Histopathological confirmation of doxorubicin-induced renal or cardiac toxicity is necessary to establish the true incidence of these complications in a population of cats receiving the drug. Without it, cats with subclinical toxicity will obviously be missed.

A limitation of this retrospective study is the heterogeneous subject population. Cats were treated with numerous chemotherapy protocols for many different types of neoplasia, and the role that administration of other chemotherapy drugs may have played is unknown. Differing treatment protocols also meant that monitoring and available follow-up information varied between animals. Repeat complete blood counts were not routinely performed at the expected nadir of leukopenia for doxorubicin, so the true incidence of neutropenia may be underestimated. Regardless of these points, however, the statistical analyses performed support the legitimacy of comparing the two study groups: there were no significant differences between groups with respect to patient age, tumor type, number of doxorubicin doses, cumulative doxorubicin dose, or other drugs administered. The primary things that differed between the two groups were individual doxorubicin dose, and the fact that cats in group B received subcutaneous fluids.

In conclusion, the results of this study suggest that there is no increased risk of toxicity associated with administration of doxorubicin to cats at an individual dose of 25 mg/m^2 given with subcutaneous fluids versus 1 mg/kg. Future studies are needed to determine if this increased dose can provide superior tumor control among cats with naturally occurring cancers. Further work must also assess the efficacy and toxicity of higher individual and cumulative doses of doxorubicin for a variety of feline tumors, both with and without the provision of fluid support.

References

Barber LG, Sorenmo KU, Cronin KL, Shofer FS (2000) Combined doxorubicin and cyclophosphamide chemotherapy for nonresectable feline fibrosarcoma. *Journal of the American Animal Hospital Association* **36**, 416–421.

Bertani T, Poggi A, Pozzoni R, Delaini F, Sacchi G, Thoua Y, Mecca G, Remuzzi G, Donati MB (1982) Adriamycin-induced nephritic syndrome in rats. *Laboratory Investigation* **46**, 16–23.

Boyer MJ, Tannock IF (2005) Cellular and molecular basis of drug treatment for cancer. In: Tannock IF, Hill RP, Bristow RG, et al (eds), *The Basic Science of Oncology* (4th edn). New York: McGraw-Hill, pp. 349–375.

Chu E, DeVita Jr VT (2001) Principles of cancer management: chemotherapy. In: DeVita Jr VT, Hellman S, Rosenberg (eds), *Cancer Principles and Practice of Oncology* (6th edn). Philadelphia: Lippincott Williams & Wilkins, pp. 289–306.

Chun R, Garrett LD, Vail DM (2007) Cancer chemotherapy. *Small Animal Clinical Oncology* (4th edn). St Louis, MO: Saunders Elsevier, pp. 163–192.

Cotter SM, Kanke PJ, Simon M (1984) Renal disease in five tumor-bearing cats treated with adriamycin. *Journal of the American Animal Hospital Association* **21**, 405–409.

Doroshow JH (2001) Anthracyclines and anthracenediones. In: Chabner BA, Longo DL (eds), *Cancer Chemotherapy and Biotherapy* (3rd edn). Philadelphia: Lippincott Williams & Wilkins, pp. 500–537.

Fajardo LF, Eltringham JR, Stewart JR, Klauber MR (1980) Adriamycin nephrotoxicity. *Laboratory Investigation* **43**, 242–253.

Henness AM, Theilen GH, Lewis JP (1977) Clinical investigation of doxorubicin, daunomycin, and 6-thioguanine in normal cats. *American Journal of Veterinary Research* **38**, 521–524.

Javiaid B, Olson JL, Meyer TW (2001) Glomerular injury and tubular loss in adriamycin nephrosis. *Journal of the American Society of Nephrology* **12**, 1391–1400.

Jeglum KA, deGuzman E, Young KM (1985) Chemotherapy of advanced mammary adenocarcinoma in 14 cats. *Journal of the American Veterinary Medical Association* **187**, 157–160.

Klimtova I, Simunek T, Mazurova Y, Hrdina R, Gersl V, Adamcova M (2002) Comparative study of chronic toxic effects of daunorubicin and doxorubicin in rabbits. *Human and Experimental Toxicology* **21**, 649–657.

Kristal O, Lana SE, Ogilvie GK, Rand WM, Cotter SM, Moore AS (2001) Single agent chemotherapy with doxorubicin for feline lymphoma: a retrospective study of 19 cases (1994–1997). *Journal of Veterinary Internal Medicine* **15**, 125–130.

Mauldin GN, Matus RE, Patnaik AK, Bond BR, Mooney SC (1988) Efficacy and toxicity of doxorubicin and cyclophosphamide used in the treatment of selected malignant tumors in 23 cats. *Journal of Veterinary Internal Medicine* **2**, 60–65.

O'Keefe DA, Schaeffer DJ (1992) Hematologic toxicosis associated with doxorubicin administration in cats. *Journal of Veterinary Internal Medicine* **6**, 276–282.

O'Keefe DA, Sisson DD, Gelberg HB, Schaeffer DJ, Krawiec DR (1993) Systemic toxicity associated with doxorubicin administration in cats. *Journal of Veterinary Internal Medicine* **7**, 309–317.

Peaston AE, Maddison JE (1999) Efficacy of doxorubicin as an induction agent for cats with lymphosarcoma. *Australian Veterinary Journal* **77**, 442–444.

Rassnick KM, Frimberger AE, Wood CA, Williams LE, Cotter SM, Moore AS (2000) Evaluation of ifosfamide for treatment of various canine neoplasms. *Journal of Veterinary Internal Medicine* **14**, 271–276.

Sui LL, Moore MJ (2005) Pharmacology of anticancer drugs. In: Tannock IF, Hill RP, Bristow RG, et al (eds), *The Basic Science of Oncology* (4th edn). New York: McGraw-Hill, pp. 322–348.

Sorenmo KU, Baez JL, Clifford CA, Mauldin E, Overley B, Skorupski K, Bachman R, Samluk M, Shofer F (2004) Efficacy and toxicity of a dose-intensified doxorubicin

protocol in canine hemangiosarcoma. *Journal of Veterinary Internal Medicine* **18**, 209–213.

Yesair DW, Schwartzbach E, Shuck D, Denine EP, Asbell MA (1972) Comparative pharmacokinetics of daunomycin and adriamycin in several animal species. *Cancer Research* **32**, 1177–1183.

Young DM (1975) Pathologic effects of adriamycin in experimental systems. *Cancer Chemotherapy Reports* **6**, 159–175.

Zwahlen CH, Lucroy MD, Kraegel SA, Madewell BR (1998) Results of chemotherapy for cats with alimentary malignant lymphoma: 21 cases. *Journal of the American Veterinary Medical Association* **213**, 1144–1149.