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# Doxorubicin: An Overview

As in human medicine, the veterinary “nurse” is a jack of all trades. A veterinary technician’s role in the oncology world is not only to have excellent technical skills but also to be warm and compassionate, be a patient advocate, and make connections with and educate clients. Treating patients with chemotherapeutics requires a thorough understanding of the risks and handling of these agents. In addition, in the face of a chemotherapeutic spill or extravasation, it is necessary to know and act on the immediate response protocol.

Doxorubicin is one of the most dangerous chemotherapeutics used in veterinary oncology. However, it is also one of the most common and efficacious treatments for several types of canine and feline malignancies (see **DOXORUBICIN IN THE TREATMENT OF SPECIFIC CANCERS**<sup>1-12</sup>).

## HISTORY

Sometimes referred to as the “red death,” doxorubicin is red in color and originates from a product of a fungus (*Streptomyces*). It is considered part of the anthracycline antitumor antibiotic class of chemotherapeutics. Its antitumor properties were first discovered more than 45 years ago, when it was being used as an antibiotic and tested on tumor-bearing mice; early dosing

**THE GREAT DANE** is a canine breed that is known to be prone to dilated cardiomyopathy. Before treatment using doxorubicin, such breeds should be evaluated by a cardiologist to search for any evidence of myocardial dysfunction.



CONTINUING  
EDUCATION

## MEET THE AUTHOR



**Emily Fullerton, RVT,  
VTS (Oncology)**

**VCA Veterinary Referral  
Associates**

**Gaithersburg, Maryland**

Emily obtained her associate’s degree from Vet Tech Institute in December 2008, leading her to her registered veterinary technician license in January 2009. She subsequently moved to Maryland, where she found her place in veterinary medicine: medical oncology. With her passion for helping animals and support from her coworkers, she achieved her Veterinary Technician Specialist certification in oncology in 2014. Emily has a love of food and wine, her own fuzzy pets, and spending time with her family.

and frequency studies were performed on dogs.<sup>13</sup> Cardiotoxic effects were first noted during human testing in the late 1960s. Fourteen children died during the study; 7 had cardiopulmonary complications.<sup>13</sup>

### CARDIOTOXIC EFFECTS

Veterinary studies of doxorubicin were first published in the late 1970s. Hundreds of published studies have since investigated its use. Clinically relevant cardiotoxicity is uncommon in cats when appropriate doses are used, but the cardiotoxic effects noted in humans have been observed in dogs (FIGURE 1). Several mechanisms for these effects have been proposed, but the most studied theory is that doxorubicin interacts and releases iron from storage proteins, causing the creation of reactive superoxide molecules, or oxidative free radicals.<sup>14</sup> The exact mechanism of iron and free radical damage as it relates to cardiotoxicity secondary to doxorubicin is unknown. Cardiac side effects of doxorubicin are cumulative and irreversible. They can occur at any time during the treatment protocol, even during administration if doxorubicin is given too quickly.<sup>15</sup> Extreme caution should be used when cumulative doses reach 180 to 240 mg/m<sup>2</sup>.

### Prevention

A few measures can be taken to help reduce the risks of doxorubicin-induced cardiomyopathy, including evaluation by a cardiologist before treatment. The cardiologist will perform such tests as echocardiography and electrocardiography (ECG) to search for

any evidence of myocardial dysfunction. This is especially recommended for breeds that are known to be prone to dilated cardiomyopathy (BOX 1). It is recommended that any patient that develops heart murmurs or arrhythmias while on doxorubicin chemotherapy be evaluated by a cardiologist.<sup>6</sup> Echocardiography and ECG are also recommended when a patient requires doses beyond the lifetime margin of safety of 180 to 240 mg/m<sup>2</sup>. A small study of the side effects of doxorubicin in cats showed that echocardiographic changes consistent with doxorubicin-induced cardiomyopathy occurred in 4 of 6 cats after cumulative doses of 170 to 240 mg/m<sup>2</sup> were given.<sup>16</sup> Because doxorubicin is usually dosed at 25 mg/m<sup>2</sup> or less for cats, and most protocols only include 4 to 5 treatments, this is not usually a clinical concern in this species.

Dexrazoxane (Zinecard; [pfizer.com](http://pfizer.com)) is a cardioprotectant intravenous drug that chelates to iron ions, thus reducing the number of ions that are available for doxorubicin to release and consequently decreasing the formation of superoxide radicals. Although this sounds like a solution to the toxic properties of doxorubicin, dexrazoxane is very expensive, and high doses need to be given to adequately protect the heart—10 times those of doxorubicin (eg, a 30 kg/0.976 m<sup>2</sup> dog would need almost 300 mg)—making it difficult for some owners to afford.<sup>17</sup>

### BOX 1 Canine Breeds Predisposed to Dilated Cardiomyopathy

- Afghan hound
- American cocker spaniel
- Boxer
- Dalmatian
- Doberman pinscher
- English cocker spaniel
- Great Dane
- Newfoundland
- St. Bernard

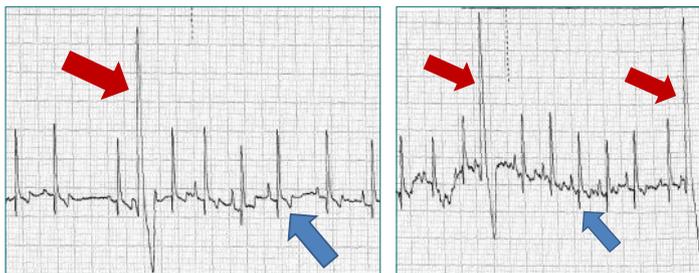


FIGURE 1. Electrocardiogram showing normal PQRST wave (blue arrows) and preventricular contractions (red arrows) caused by doxorubicin.

● **TECHPOINT** ●

A veterinary technician's role in the oncology world is not only to have excellent technical skills but also to also be warm and compassionate, be a patient advocate, and make connections with and educate clients.

Dexrazoxane is available in 250 and 500 mg sterile vials and is reconstituted with sodium lactate to a concentration of 10 mg/mL.<sup>18</sup> The patient dose is then further diluted with sterile 0.9% NaCl or 5% dextrose solution to a concentration of 1.3 to 5 mg/mL.<sup>19</sup> The infusion is given intravenously over 15 minutes, and doxorubicin administration should follow within 30 minutes of finishing the infusion.

**ADMINISTRATION**

Doxorubicin must always be administered through a clean, "one stick" intravenous catheter. The vein being used should be intact and should not have been used within the 24 to 48 hours before doxorubicin administration. Doxorubicin is diluted with sterile 0.9% sodium chloride or 5% dextrose solution; the dilution ratio may vary by hospital. The vein should be continually monitored for any sign of extravasation, and blood drawback confirmation is necessary before every push of doxorubicin. Institutions administering doxorubicin must have an extravasation protocol and easy access to the supplies needed to carry it out, including dexrazoxane.

To avoid acute adverse effects, doxorubicin is administered as a carefully controlled slow infusion, generally over 15 to 20 minutes. Adverse

effects can include acute vomiting, nausea, hives, blood pressure changes, and arrhythmias and are attributed to an anaphylactic response and a release of histamine. During doxorubicin administration, it is the veterinary technician's responsibility to be alert and in tune with the patient's demeanor. Noticing a change in the patient's behavior during administration could mean catching an acute side effect before it manifests and reversing it. Patients experiencing acute side effects may hypersalivate; become restless or lethargic; have pale or injected mucous membranes; develop hives, facial swelling, or wheals; or vomit. A general guideline for veterinary technicians administering doxorubicin is to know the patient and be alert to any changes during doxorubicin administration. If an anaphylactic response is suspected, the administration of doxorubicin should be paused. Administration of an antihistamine (diphenhydramine 3–4 mg/kg IM), and a corticosteroid (dexamethasone sodium phosphate 0.5–1 mg/kg IV) is recommended.<sup>17</sup> The doxorubicin administration can be finished, at a much slower rate, when the patient's clinical signs subside. When doxorubicin is administered at a slow rate, acute adverse effects are infrequent.

Before initiation of doxorubicin treatment, baseline staging tests such as a complete blood cell count, serum chemistry, and urinalysis should be performed. Doxorubicin should be used with caution in feline patients with known renal dysfunction.<sup>16</sup> Doses can be reduced in these patients, but judicious monitoring of renal values and urine concentration is recommended, ideally before administration of each dose.

**EXTRAVASATION**

Doxorubicin tissue extravasation has the potential to be catastrophic. This is one of the main reasons that only trained personnel should handle doxorubicin. Extravasation, or leaking of a drug outside of a vein, of some chemotherapeutics can cause mild to moderate tissue irritation, but doxorubicin can cause tissue sloughing, necrosis, and wounds that can take months to heal and may require amputation.

## BOX 2 Doxorubicin Extravasation Protocol

1. Without removing the IV catheter, draw back as much of the chemotherapy agent as possible.
2. Remove catheter.
3. Apply cold compress for 15-minute periods every 4 to 8 hours for the first 24 hours.
4. Place an IV catheter in a different vein to administer dexrazoxane\*:
  - a. Within the first 2 hours
  - b. 24 hours after extravasation
  - c. 48 hours after extravasation

### Other considerations:

- Send all patients home with Elizabethan collars
- Apply Synotic (DMSO) to the area
- Consider NSAIDs and other pain medications for these patients

\*Dexrazoxane is dosed at 10 times the dose of doxorubicin, diluted with 0.9% NaCl at a ratio of 1:1, and given over 15 minutes.

Veterinary technicians who handle doxorubicin must understand the emergency procedures necessary in the event of extravasation, including the dose, proper administration, and availability of dexrazoxane. If extravasation is suspected, the doxorubicin infusion should be terminated and every attempt made to draw back as much of the doxorubicin product from the catheter as possible before the catheter is removed. Application of a cold compress promotes vasoconstriction and decreases diffusion of doxorubicin into the surrounding tissues. The dosing and dilution ratio of dexrazoxane are the same as if it is being used for its cardioprotective properties.

In a small study of 4 dogs with doxorubicin extravasation, 3 patients showed resolution of lesions with medical management alone after

## • TECHPOINT •

Veterinary technicians who handle doxorubicin must understand the emergency procedures necessary in the event of extravasation, including the dose, proper administration, and availability of dexrazoxane.

the extravasation was treated with dexrazoxane within 2 hours.<sup>20</sup> Repeated doses at 24 and 48 hours after the event may also improve outcome. To prevent additional trauma that will perpetuate the wound, an Elizabethan collar is advised. Administration of NSAIDs and pain medications should be considered. Application of a cold compress to the area for periods of 15 minutes multiple times during the first 24 hours may also help mitigate the effects of doxorubicin extravasation.

The benefits of applying topical dimethyl sulfoxide (DMSO) to the area of extravasation are unclear. However, DMSO is recommended by many oncologists in the event of an extravasation for the following reasons<sup>20</sup>:

- It decreases pain by blocking nerve conduction fibers.
- It reduces inflammation and swelling.
- It improves blood supply and oxygen delivery via its vasodilation properties.
- It is one of the most potent free radical scavengers.

**BOX 2** provides an example of an extravasation protocol.

## ADVERSE EFFECTS

Doxorubicin has the potential to cause some of the most severe delayed adverse effects of any drug in veterinary oncology. In general, delayed effects can be grouped into gastrointestinal, hematologic, organ toxicosis, and other. Most adverse effects can be handled with ancillary medications that the owners can give at home. In fact, <5% of patients have side effects so severe that they need to be hospitalized. In an effort to help veterinary oncologists quantify chemotherapy toxicities, or adverse events, the Veterinary Cooperative Oncology Group (VCOG) has established grading criteria for different types of adverse events (TABLE 1).<sup>21</sup> This grading system helps the veterinary

oncology team work with owners to decide the severity of the event (eg, vomiting, diarrhea, inappetence) and helps oncologists make treatment recommendations and decisions.

## Gastrointestinal

The gastrointestinal tract is lined with rapidly dividing cells, much like those of malignant tumors. Doxorubicin, like most chemotherapeutics, is designed to target such cells, leaving the gastrointestinal tract open to its effects. Vomiting, nausea, inappetence, and diarrhea are among the gastrointestinal side effects associated with doxorubicin administration. They usually occur anywhere from 2 to 5 days after administration. The addition of maropitant (Cerenia; [zoetis.com](http://zoetis.com)) to the ancillary medications

**TABLE 1 Gastrointestinal Adverse Events Associated With Chemotherapy**

Adverse Event	GRADE				
	I	II	III	IV	V
<b>Neutropenia</b>	1500 uL to <LLN	1000–1499 uL	500–999 uL	<500 uL	Death
<b>Anorexia: Disorder characterized by loss of appetite</b>	Coaxing or dietary change required to maintain appetite	Oral intake altered ( $\leq 3$ days) without significant weight loss; oral nutritional supplements/appetite stimulants may be indicated	Of >3 days' duration; associated with significant weight loss ( $\geq 10\%$ ) or malnutrition; IV fluids, tube feeding, or force feeding indicated	Life-threatening consequences; TPN indicated; >5 days' duration	Death
<b>Diarrhea: Disorder characterized by frequent, watery bowel movements</b>	Increase of up to 2 stools per day over baseline; no increase in frequency; however, consistency decreased over baseline	Increase of 3–6 stools per day over baseline; medications indicated; parenteral (IV or SC) fluids indicated $\leq 48$ h; not interfering with ADL	Increase of >6 stools per day over baseline; incontinence >48 h; IV fluids >48 h; hospitalization; interfering with ADL	Life-threatening (eg, hemodynamic collapse)	Death
<b>Nausea/ptyalism: Disorder characterized by hypersalivation and sensation or urge to vomit; difficult to assess in companion species</b>	Loss of appetite without alteration in eating habits	Salivation or lip smacking <3 days' duration, grade 2 anorexia	Salivation or lip smacking >3–5 days' duration, grade 3 anorexia	Salivation or lip smacking >5 days' duration, grade 4 anorexia	—
<b>Vomiting: Disorder characterized by the reflexive act of ejecting the contents of the stomach through the mouth</b>	<3 episodes in 24 h; medical intervention not indicated	3–10 episodes in 24 h; <5 episodes/day for $\leq 48$ h; parenteral fluids (IV or SC) indicated $\leq 48$ h; medications indicated	Multiple episodes >48 h and IV fluids or PPN/TPN indicated >48 h	Life-threatening (eg, hemodynamic collapse)	Death

ADL, activities of daily living (eating, sleeping, urinating, defecating); LLN, lower limit of normal; PPN, partial parenteral nutrition; TPN, total parenteral nutrition.

Adapted with permission from Veterinary Cooperative Oncology Group—common terminology criteria for adverse events (VCOG-CTCAE) following chemotherapy or biological antineoplastic therapy in dogs and cats v1.1. Vet Comp Oncol doi: 10.1111/j.1476-5829.2011.00283.x.

# Doxorubicin in the Treatment of Specific Cancers

Doxorubicin is what some might refer to as the “broad-spectrum” chemotherapy drug of choice in veterinary oncology. It has potential antagonistic properties against 3 broad categories of tumors: round cell tumors, mesenchymal tumors, and epithelial tumors. Within these categories fall some of the most common canine and feline malignancies, including lymphoma, hemangiosarcoma, and mammary gland carcinoma. Doxorubicin provides a clinical benefit in each of these types of cancer.

## LYMPHOMA

Canine high-grade lymphoma is one of the most treatable cancers in veterinary oncology. The most common presentation is the multicentric form, which is characterized by the presence of superficial lymphadenopathy. Although lymphoma is seen often, the treatment has not made many advances in recent years. One thing that has stayed the same is that doxorubicin is the most effective drug against high-grade lymphoma when used in a single-agent protocol. This is most significant for dogs that have B-cell lymphoma. A single-agent chemotherapy protocol uses one drug in a regimen given over a certain amount of time. In this case, doxorubicin is administered every 14 to 21 days to patients for a total of 5 or 6 treatments (10–18 weeks). When this protocol is used, median patient survival times can reach 7 to 9 months, and 70% of patients go into clinical remission.<sup>1</sup>

Single-agent protocols, although effective, do not produce the high response rates of more aggressive therapy, such as multiagent chemotherapy protocols. Of the many multiagent protocols for lymphoma, the most popular is called *CHOP*, which is an acronym for cyclophosphamide, hydroxydaunorubicin (doxorubicin), Oncovin (vincristine), and prednisone. It has many variations. Multiagent chemotherapy protocols can induce remission in 80% to 95% of cases of high-grade canine lymphoma, with median survival times of 10 to 12 months. Of those patients, 20% to 25% will be alive 2 years after initiation of chemotherapy.<sup>2</sup> Most multiagent chemotherapy protocols comprise weekly to biweekly chemotherapy treatments for an average of 16 to 20 weeks.

Feline lymphoma has multiple presentations, the most common being nasal and gastrointestinal

lymphoma (high or low grade). Other forms of lymphoma in cats include mediastinal, peripheral nodal, renal, and laryngeal. Unlike in dogs, single-agent doxorubicin has not proven to be a successful treatment for feline lymphoma. This fact, in addition to the potential for renal toxicity, makes multiagent chemotherapy, with the same cycle of drugs as that used in canine patients, the gold standard for feline lymphoma. Unfortunately, most forms of feline lymphoma do not have the same response rates and remission times as canine lymphoma. Cats with high-grade gastrointestinal lymphoma that receive the multiagent chemotherapy protocol can achieve remission rates of 50% to 80% and median survival times of 6 to 9 months.<sup>3</sup>

## MESENCHYMAL TUMORS

Mesenchymal tumors, such as hemangiosarcoma, osteosarcoma, and high-grade soft tissue sarcomas, are very aggressive and highly metastatic tumors in dogs. The treatment of choice for these types of tumors is always to control and diminish the amount of local disease. Aggressive surgeries such as splenectomy, amputation, and aggressive mass resection are the best approaches. However, once a patient’s tumor burden is reduced to microscopic disease, doxorubicin chemotherapy can be initiated.

Doxorubicin is most effective for treatment of mesenchymal tumors when the tumor burden is at a microscopic level. Left untreated, tumors eventually outgrow their natural blood supply. As a result, the center of the tumor often becomes hypoxic, inhibiting the ability for cytotoxic drugs, such as doxorubicin, to reach these neoplastic cells. Cytotoxic drugs may, however, have some short-lived effects against the outermost tumor cells.

If a surgical site is not quite healed, doxorubicin can still be safely administered as long as the site is clean and healthy. Doxorubicin itself does not delay wound healing, but the myelosuppressive side effects of doxorubicin could delay an immune response if an infection occurs. Single-agent doxorubicin protocols used against mesenchymal tumors are similar to those for lymphoma.

Although mesenchymal tumor types are in a single class of malignancies, their disease processes and outcomes are very different.

### Hemangiosarcoma

Hemangiosarcomas, tumors arising from lining of blood vessels, account for 12% to 21% of all canine mesenchymal neoplasms.<sup>4</sup> The most common site of origin is the spleen, although they also arise in the right atrium, skin and subcutis, and liver.<sup>4</sup> Most patients present with lethargy, decreased appetite, distended abdomen, and collapse and are likely experiencing blood loss due to a ruptured splenic tumor. However, not all bleeding splenic tumors are malignant. Approximately two-thirds of dogs with splenic masses have a malignant tumor, and approximately two-thirds of those tumors are hemangiosarcoma (the "double two-thirds rule"). Although surgery is the first step in treating splenic hemangiosarcoma, survival times with surgery alone only reach 1 to 3 months. Chemotherapy is recommended as a follow-up treatment for microscopic disease. Single-agent doxorubicin (30 mg/m<sup>2</sup> IV every 2–3 weeks) has been shown to increase survival times to 5 to 6 months.<sup>5</sup>

### Osteosarcoma

Canine osteosarcoma is the most common type of primary bone tumor, accounting for >85% of skeletal tumors. Amputation should be considered palliative care only for patients with osteosarcoma of the axial skeleton. This procedure removes the source of pain, but does not address the high metastatic rates. Pulmonary metastases are found on presurgical radiographs in approximately 10% of patients, but because lesions must be 4 to 6 mm in diameter to be visible on radiographs, it is thought that most patients have micrometastases at the time of surgery. Chemotherapy is therefore recommended after amputation.<sup>6</sup>

Protocols containing platinum drugs, such as carboplatin, are considered front-line therapy, giving patients median survival times of 9 to 12 months with minimal adverse effects (250–300 mg/m<sup>2</sup> IV every 3 weeks for 4–6 treatments<sup>7</sup>), but single-agent doxorubicin has been shown to have some cytotoxic effect against canine osteosarcoma. In one study,<sup>8</sup> the best responses to doxorubicin were seen when it is administered every 2 weeks at 30 mg/m<sup>2</sup>, with 2 to 3 doses administered before amputation and the remaining 3 to

4 doses afterward. Median survival times of patients in this study were just over 1 year, with about 50% of patients alive at 1 year after diagnosis, and just under 10% alive at 2 years.

### Soft Tissue Sarcoma

Soft tissue sarcoma (STS) is a broad category of malignancies in dogs and cats, comprising 15% of all dermal tumors and 7% of all subcutaneous tumors in these species.<sup>9</sup> STS may be classified as high grade or low grade. Low-grade STS are locally invasive tumors with low metastatic rates. These tumors can be cured with aggressive surgery with or without radiation therapy. High-grade STS are locally invasive, with metastatic rates that can reach 44%.<sup>10,11</sup> Doxorubicin and ifosfamide are used for human STS, but response rates only reach 30%, and single-agent and multiagent protocols have not shown a significant increase in overall survival times compared to surgery alone. They do, however, help improve disease-free survival times. The role of adjuvant chemotherapy after surgery for high-grade STS in dogs is yet to be determined, but as with any high-grade tumor with high metastatic rates, it should be considered.

### EPITHELIAL TUMORS

Doxorubicin is considered in the treatment of epithelial tumors such as mammary gland carcinoma. Mammary gland tumors are one of the most common neoplasms in sexually intact female dogs, but the incidence rate in the United States is lower than many other countries, likely due to our early ovariohysterectomy practices.<sup>12</sup> As for most solid tumors, surgery is the first recommendation for tumor control. Many oncologists make their decisions on the need for follow-up chemotherapy based on tumor size, grade, and the presence or absence of lymphatic invasion/lymph node involvement.

Studies have yet to show a clear survival or disease-free benefit from incorporating doxorubicin chemotherapy in the treatment of patients with large or multiple high-grade tumors with lymph node or pulmonary metastases. However, veterinary oncology often refers to the treatment of women with advanced or metastatic breast cancer with doxorubicin-based protocols.

regimen after doxorubicin administration has been shown to decrease the number of patients that experience vomiting and diarrhea, and to lessen the severity of these effects in patients that do experience them.<sup>22</sup> Patients in this study received maropitant (2 mg/kg) orally for 5 consecutive days after doxorubicin administration. Alternatively, maropitant can be given orally or subcutaneously before doxorubicin administration, followed by 4 consecutive daily doses at home. This is simpler because of the way maropitant is packaged. Fasting patients before treatment with doxorubicin has also been shown to reduce the incidence of vomiting after treatment.<sup>23</sup>

Diarrhea is another known adverse effect of doxorubicin that can manifest in the first week after administration. Metronidazole can be used to help these patients at doses as low as 10 mg/kg PO every 12 hours as needed for soft stool or diarrhea.<sup>19</sup> If soft stool or diarrhea does not respond to metronidazole therapy, alternative options include tylosin and probiotics. Veterinary oncology technicians should be well versed in adverse gastrointestinal effects and recommended therapy so that they can accurately discuss these details with owners.

### Hematologic

Doxorubicin's myelosuppressive effects, which are described as mild to moderate, are one of its many dose-limiting toxicities; the established dose of doxorubicin is based on the increased rate of myelosuppression at higher doses. A complete blood cell count with differentials should be performed 7 to 10 days after doxorubicin administration to monitor for white blood cell (specifically neutrophil) nadirs. The nadir is defined as the anticipated lowest cell count in a patient after chemotherapy. Neutropenia after doxorubicin administration can be dangerous because of the potential for simultaneous adverse gastrointestinal effects. Vomiting and/or diarrhea can cause translocation of bacteria, and if a patient's immune response is compromised, sepsis may occur.<sup>17</sup> Other, less common hematologic effects of doxorubicin include anemia and thrombocytopenia.

Prophylactic antibiotics may be considered after a patient's first dose of doxorubicin. In dogs, sulfamethoxazole–trimethoprim is a broad-spectrum, cost-effective, relatively safe antibiotic that is gentle on the gastrointestinal tract. It can be started 3 days after doxorubicin infusion and continued for 7 days, or longer as needed (15–30 mg/kg PO BID).<sup>19</sup> Doxorubicin-associated neutropenia is less common in cats, and client administration of oral medications to cats can decrease quality of life for both client and patient, so a prophylactic antibiotic can be spared in feline patients.

### Other

Most veterinary patients do not experience the same chemotherapy-induced alopecia as human patients, but patchy alopecia may be seen in breeds with continually growing hair (eg, Maltese, golden retrievers, poodles). It mostly affects the hair around the muzzle and eyes, but severe cases of hair loss can occur (**FIGURE 2**). To help prevent painful



**FIGURE 2.** A bichon showing the extreme effects of doxorubicin-induced alopecia.

• **TECHPOINT** •

Although doxorubicin poses significant risks in administration and toxicity, it is one of the most effective chemotherapeutic agents in veterinary medicine.

matting of the fur, it is recommended to keep patients undergoing chemotherapy well groomed. Hyperpigmentation of the skin of shaved and thinly haired areas can occur (**FIGURE 3**). Radiation recall dermatitis (RRD) is a phenomenon in humans in which the dermal side effects of radiation return



**FIGURE 3.** A golden retriever showing the expected alopecia and hyperpigmentation effects of doxorubicin administration.

if certain chemotherapeutic agents are administered shortly after radiation therapy is completed. Cases of RRD have been reported up to 2 decades after radiation therapy.<sup>24</sup> This phenomenon is not reported in veterinary patients, but many believe it can occur.

**CONCLUSION**

Although doxorubicin poses significant risks in administration and toxicity, it is one of the most effective chemotherapeutic agents in veterinary medicine. Its effects help patients achieve lengthy and good quality of life remission and survival times for many types of malignancies. Doxorubicin's potential benefits almost always outweigh the risks of its adverse effects. Doxorubicin is a drug that requires meticulous attention to detail and exceptional technical skills. Staff members handling doxorubicin should be well versed

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**Caution**

Federal (USA) law restricts this drug to use by or on the order of a licensed veterinarian.

**Indications**

SENTINEL<sup>®</sup> SPECTRUM<sup>®</sup> (milbemycin oxime/lufenuron/praziquantel) is indicated for the prevention of heartworm disease caused by *Dirofilaria immitis*; for the prevention and control of flea populations (*Ctenocephalides felis*); and for the treatment and control of adult roundworm (*Toxocara canis*, *Toxascaris leonina*), adult hookworm (*Ancylostoma caninum*), adult whipworm (*Trichuris vulpis*), and adult tapeworm (*Taenia pisiformis*, *Echinococcus multilocularis* and *Echinococcus granulosus*) infections in dogs and puppies two pounds of body weight or greater and six weeks of age and older.

**Dosage and Administration**

SENTINEL SPECTRUM should be administered orally, once every month, at the minimum dosage of 0.23 mg/lb (0.5 mg/kg) milbemycin oxime, 4.55 mg/lb (10 mg/kg) lufenuron, and 2.28 mg/lb (5 mg/kg) praziquantel. For heartworm prevention, give once monthly for at least 6 months after exposure to mosquitoes.

**Dosage Schedule**

Body Weight	Milbemycin Oxime per chewable	Lufenuron per chewable	Praziquantel per chewable	Number of chewables
2 to 8 lbs.	2.3 mg	46 mg	22.8 mg	One
8.1 to 25 lbs.	5.75 mg	115 mg	57 mg	One
25.1 to 50 lbs.	11.5 mg	230 mg	114 mg	One
50.1 to 100 lbs.	23.0 mg	460 mg	228 mg	One
Over 100 lbs.	Administer the appropriate combination of chewables			

To ensure adequate absorption, always administer SENTINEL SPECTRUM to dogs immediately after or in conjunction with a normal meal.

SENTINEL SPECTRUM may be offered to the dog by hand or added to a small amount of dog food. The chewables should be administered in a manner that encourages the dog to chew, rather than to swallow without chewing. Chewables may be broken into pieces and fed to dogs that normally swallow treats whole. Care should be taken that the dog consumes the complete dose, and treated animals should be observed a few minutes after administration to ensure that no part of the dose is lost or rejected. If it is suspected that any of the dose has been lost, re-dosing is recommended.

**Contraindications**

There are no known contraindications to the use of SENTINEL SPECTRUM.

**Warnings**

Not for use in humans. Keep this and all drugs out of the reach of children.

**Precautions**

Treatment with fewer than 6 monthly doses after the last exposure to mosquitoes may not provide complete heartworm prevention.

Prior to administration of SENTINEL SPECTRUM, dogs should be tested for existing heartworm infections. At the discretion of the veterinarian, infected dogs should be treated to remove adult heartworms. SENTINEL SPECTRUM is not effective against adult *D. immitis*.

Mild, transient hypersensitivity reactions, such as labored breathing, vomiting, hypersalivation, and lethargy, have been noted in some dogs treated with milbemycin oxime carrying a high number of circulating microfilariae. These reactions are presumably caused by release of protein from dead or dying microfilariae.

Do not use in puppies less than six weeks of age.

Do not use in dogs or puppies less than two pounds of body weight.

The safety of SENTINEL SPECTRUM has not been evaluated in dogs used for breeding or in lactating females. Studies have been performed with milbemycin oxime and lufenuron alone.

**Adverse Reactions**

The following adverse reactions have been reported in dogs after administration of milbemycin oxime, lufenuron, or praziquantel: vomiting, depression/lethargy, pruritus, urticaria, diarrhea, anorexia, skin congestion, ataxia, convulsions, salivation, and weakness.

To report suspected adverse drug events, contact Virbac at 1-800-338-3659 or the FDA at 1-888-FDA-VETS.

**Information for Owner or Person Treating Animal**

*Echinococcus multilocularis* and *Echinococcus granulosus* are tapeworms found in wild canids and domestic dogs. *E. multilocularis* and *E. granulosus* can infect humans and cause serious disease (alveolar hydatid disease and hydatid disease, respectively). Owners of dogs living in areas where *E. multilocularis* or *E. granulosus* are endemic should be instructed on how to minimize their risk of exposure to these parasites, as well as their dog's risk of exposure. Although SENTINEL SPECTRUM was 100% effective in laboratory studies in dogs against *E. multilocularis* and *E. granulosus*, no studies have been conducted to show that the use of this product will decrease the incidence of alveolar hydatid disease or hydatid disease in humans. Because the prepatent period for *E. multilocularis* may be as short as 26 days, dogs treated at the labeled monthly intervals may become reinfected and shed eggs between treatments.

Manufactured for: Virbac AH, Inc.

P.O. Box 162059, Ft. Worth, TX 76161

NADA #141-333, Approved by FDA

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in the potential adverse effects to be able to comfort and educate owners of pets going through chemotherapy. ■

**References**

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