Journal of Veterinary Internal Medicine

Journal of Veterinary Internal Medicine Open Access
ACVIM American College of Veterinary Internal Medicine

STANDARD ARTICLE OPEN ACCESS

Small Animal Internal Medicine Oncology

A Retrospective Study of Chemotherapy-Related Extravasation Events in Dogs and Cats

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Received: 30 August 2024 | **Revised:** 12 February 2025 | **Accepted:** 21 February 2025

Funding: The authors received no specific funding for this work.

Keywords: adverse events | cat | dog | extravasation | veterinary

ABSTRACT

Background: Chemotherapy extravasation is a potentially serious complication. There is a paucity of information in the veterinary literature investigating extravasation events, treatments, and outcomes.

Objective: Evaluate chemotherapy extravasation events and treatments in dogs and cats, adverse events (AEs), and overall outcomes.

Animals: Twenty dogs and three cats were included.

Methods: Retrospective, multicenter, descriptive study including dogs or cats with suspected extravasation from chemotherapy. Information obtained included: signalment, extravasation details and treatment provided, AEs graded according to VCOG-CTCAE v2 criteria, and outcome.

Results: The most common drug extravasated was doxorubicin, followed by carboplatin. Carboplatin extravasation ($n = 5$) resulted in Grades III–IV AEs, all of which required surgical debridement. Doxorubicin extravasation ($n = 9$) resulted in Grades 0–V AEs, two of which amputation was ultimately recommended, and one of those two was euthanized instead. Extravasation of vinca alkaloids ($n = 5$) and rabacfosadine ($n = 1$) resulted in Grades II–III AEs, all managed in the outpatient setting. Mitoxantrone ($n = 2$) and dacarbazine ($n = 1$) extravasation resulted in no clinical signs associated with extravasation injury. Seventy-eight percent (18/23) cases had extravasation occur during one of the first four treatments of chemotherapy, with 30% (7/23) occurring during the first chemotherapy treatment.

Conclusions and Clinical Importance: Most cases (20/23) had mild to moderate or no AEs. Findings support that carboplatin should be considered a vesicant.

Abbreviations: AE, adverse event; DMSO, dimethylsulfoxide; EE, extravasation event; ET, extravasation treatment; VCOG-CTCAE v2, Veterinary Cooperative Oncology Group—common terminology criteria for adverse events volume 2.

1 | Introduction

Extravasation is defined as the inadvertent leakage of a drug from a vein into surrounding tissue, and the degree of tissue injury is determined by the drug's classification as an irritant, vesicant, or non-vesicant [1, 2]. Irritants have the potential to cause an inflammatory reaction but generally not tissue damage, whereas vesicants can cause tissue injury and necrosis [1]. Examples of irritant chemotherapies include dacarbazine and carboplatin [3]. Examples of vesicant chemotherapies include doxorubicin, vinca alkaloids, rabacfosadine, and actinomycin-D [3, 4]. Mitoxantrone is typically categorized as an irritant, however some reports classify it as a vesicant based on concentration and volume [1, 5–7]. The severity of tissue damage secondary to extravasation might be related to the drug's DNA binding properties, as this can make it more difficult to remove the drug from the tissues [1, 2]. DNA binding chemotherapy drugs include doxorubicin and mitoxantrone [1, 2]. Vinca alkaloids are classified as non-DNA binding drugs [1, 2]. There are several known risk factors for extravasation injury reported in people, including, but not limited to, the presence of small veins, recent venipuncture in the same vein, use of large-gauge catheters or butterfly catheters, and age (very young or elderly) [3, 5–7]. Additionally, drug-related extravasation risk factors can include the concentration of the drug, the volume extravasated, and the location of extravasation [5–7]. In people, common clinical signs of irritant injury include swelling, pain, discomfort, and erythema, while signs of vesicant injury can also include ulceration and necrosis [2].

There is a paucity of information in the veterinary literature on the treatment and outcome of chemotherapy extravasation injury. Publications evaluating extravasation injury or treatment response consist of single case reports or small case series [8–12]. A study published by Miller et al. described suspected carboplatin extravasation in seven dogs [8]. Of these dogs, six developed full-thickness necrosis around the vessel, and three had swelling and edema in the same region [8]. The wounds completely healed in six of the seven dogs, a median of 25.5 days after observation of extravasation injury [8]. Venable et al. published a case series describing the outcomes of four dogs with known or suspected doxorubicin extravasation receiving the neutralizing agent dexrazoxane [9]. In three dogs, complications were noted during the infusion of doxorubicin, and dexrazoxane was administered within 2 h, based on recommendations from physician-based medicine [9]. In the fourth dog, dexrazoxane was not administered until 48 h after infusion, when clinical signs of a suspected extravasation injury were noted [9]. This latter case was the only dog that developed extensive limb necrosis requiring amputation [9].

The aim of this retrospective, multicenter, descriptive study was to evaluate chemotherapy extravasation events (EEs) in dogs and cats, subsequent adverse events (AEs), and overall outcomes. To our knowledge, this is the largest descriptive study of chemotherapy extravasation injuries in veterinary medicine.

2 | Materials and Methods

Records were gathered from contributing institutions through direct contact and contact through the American College of Veterinary Internal Medicine, Oncology listserv. Contributors either completed a data sheet electronically or provided a copy of the medical records for review by the primary and corresponding author. Canine and feline cases were included if they had a suspected EE during the administration of chemotherapy.

Medical records were reviewed retrospectively. Information related to signalment, tumor type, EE, treatment of the extravasation injury, and outcome was obtained from the records. Table 1 provides details of the information obtained. The severity of the lesion resulting from the EE was graded retrospectively according to the Veterinary Cooperative Oncology Group—common terminology criteria for AEs (VCOG-CTCAE v2) following investigational therapy in dogs and cats [13]. Table 2 depicts the grading scores and associated clinical changes for chemotherapy extravasation injury as described elsewhere [13]. VCOG-CTCAE v2 does not describe a Grade 0 AE. Grade 0 was used in our study to describe a case in which no clinical signs of extravasation injury were reported after known extravasation.

3 | Results

3.1 | Case and Tumor Demographics

Twenty-three cases met the inclusion criteria, including 20 dogs and three cats. Case and tumor demographics are summarized in Table 3. Dog breeds represented included Labrador retriever ($n = 3$), mixed breed dog ($n = 3$), Golden retriever ($n = 2$), Jack Russell terrier ($n = 2$), Rottweiler ($n = 2$), and one each of the following: Shih Tzu, Great Pyrenees, Staffordshire bull terrier, Keeshond, Vizsla, Bernese mountain dog, German shepherd, and Greyhound. Cat breeds represented included one each of Ragdoll, Tonkinese, and domestic short hair.

3.2 | Extravasation Events

EE data as it relates to each case is summarized in Table S1. The EE occurred during the first chemotherapy administration in 7/23 (30%) of cases. Drugs extravasated in this group included: carboplatin ($n = 2$), doxorubicin ($n = 2$), and one each of mitoxantrone, vincristine, and vinorelbine. The EE occurred during the second, third, or fourth chemotherapy administration in 11/23 (48%) cases. Drugs extravasated in this group included: doxorubicin ($n = 4$), carboplatin ($n = 3$), and one each of mitoxantrone, rabacfosadine, vinblastine, and vincristine. The EE occurred during the fifth or subsequent chemotherapy administration in 5/23 (22%) cases. Drugs extravasated in this group included: doxorubicin ($n = 3$) and one each of dacarbazine and vincristine. The range of chemotherapy administrations before EE for all cases was 0–14. The most common drug that was extravasated was doxorubicin ($n = 9$), followed by carboplatin ($n = 5$), vincristine ($n = 3$), mitoxantrone ($n = 2$), and one each of dacarbazine, rabacfosadine, vinblastine, and vinorelbine. The most common location of extravasation was the left forelimb ($n = 11$), followed by the right hindlimb ($n = 5$), the right forelimb ($n = 4$), the left hindlimb ($n = 2$), and the ventral abdomen during intracavitary infusion ($n = 1$). An intravenous catheter was used for most cases (21/23), with the remaining cases using a butterfly catheter ($n = 1$, carboplatin) and an intravenous catheter placed into the

TABLE 1 | Information retrospectively obtained from the medical records.

Signalment	Tumor information	Extravasation event (EE)	Extravasation treatment (ET)	Outcome
Species	Tumor type	Date of EE	Attempt to aspirate back	Time to resolution
Dog	Date diagnosed	Drug extravasated	Yes	Short-term AEs
Cat		Drug dilution	No	Long-term AEs
Breed		Yes	Compress used	Date chemo discontinued
Age		No	Type (warm or cold)	Reason for discontinuation
Sex		Drug volume extravasated, estimated	Neutralizing agent used:	Date of death
Neuter status		Extravasation location	Type	
Body weight		# injectable chemo before EE	Dose	
		Administration methods	Frequency of administration	
		IV manual bolus	Outpatient or inpatient	
		Infusion manual slow push	Oral or injectable medications	
		IV fluid pump assisted infusion	Pain/inflammation	
		IV catheter	Infection	
		Butterfly catheter	Antihistamine	
		Catheter size	Topical medications	
		Sedation/anesthesia use	Surgical debridement	
		Yes or no and type	Bandage use	
		Oral sedatives	Limb amputation	
		Injectable sedatives		
		General anesthesia		
		Skill level of personnel		
		General practice (GP) tech or clinician		
		Specialty Vet Tech (SVT) or clinician		

TABLE 2 | Veterinary cooperative oncology group—common terminology criteria for adverse events (VCOG-CTCAE v2) following investigational therapy in dogs and cats.

	Grade I	Grade II	Grade III	Grade IV	Grade V
Infusion site extravasation/ reaction[a]	Swelling including edema but without erythema or pain	Erythema with associated signs (e.g., edema, pain, induration, phlebitis)	Ulceration or necrosis: severe tissue damage; surgical intervention indicated (soft tissue debridement or repair)	Life-threatening consequences (euthanasia will be performed without intervention); wound that shows no evidence of healing or improvement over 2 weeks; urgent and extreme intervention indicated (such as limb amputation)	Death

Note: The grading of the adverse event of infusion site extravasation. In this reference, extravasation is defined as a disorder characterized by the leakage of a pharmacological substance from the infusion site into the surrounding tissues. This table is provided as a convenient reference for the reader. Please see the full reference for additional information [13].

[a]The VCOG-CTCAE v2 does not describe "Grade 0" adverse events. Grade 0 was used in our study to describe a case in which no clinical signs of extravasation injury were reported after known extravasation.

peritoneal space for intracavitary chemotherapy administration ($n = 1$, mitoxantrone). Catheter size was reported in 10/22 cases, eight of which were 22-gauge catheters (including: doxorubicin [$n = 4$], carboplatin [$n = 2$], and mitoxantrone [$n = 2$]) and two of which were 25-gauge catheters (one each of doxorubicin and vincristine). Chemotherapy was administered by manual slow push ($n = 15$), manual bolus ($n = 4$), or fluid pump-assisted infusion ($n = 2$). The latter two cases in which fluid pump-assisted infusion was used included one each of doxorubicin and dacarbazine. The administration technique was not reported in two

TABLE 3 | Case and tumor demographics summarized.

	Number
Species	
Dog	20
Cat	3
Age	
Range	3–15 years
Sex	
Female spayed	8
Male neutered	14
Male intact	1
Bodyweight	
Range	2.55–66.4 kg
Median	29 kg
Tumor type	
Lymphoma	10
Osteosarcoma (including extraskeletal)	5
Hemangiosarcoma	2
Urothelial carcinoma	1
Carcinomatosis	1
Mast cell tumor	1
Collision (thymoma and osteosarcoma)	1
Pulmonary adenocarcinoma	1
Mammary carcinoma	1

cases. Chemotherapy was diluted before administration in 13/23 (57%) of cases. Dilution was reported in 8/9 doxorubicin treatments, 2/2 mitoxantrone treatments, and each single dose of rabacfosadine, vinorelbine, and dacarbazine. Dilution did not occur for the following administrations: carboplatin ($n = 5/5$), vincristine ($n = 3/3$), and one each of doxorubicin (1/9, Case 9 on Table S1) and vinblastine (1/1). Nineteen cases were fully awake and received no form of injectable nor oral sedatives before chemotherapy administration. One case (Case 9) received dexmedetomidine injectable sedation before doxorubicin administration. The use or lack of sedation was not reported in three cases (Cases 12, 15, 18). The volume of extravasated drug was estimated in nine cases and not reported in 14 cases. In two cases, it was estimated that the majority of doxorubicin administered was extravasated; one case (Case 11) developed Grade IV and the other (Case 7) Grade V AEs, despite treatment with the neutralizing agent dexrazoxane in both cases. An estimated 75% of carboplatin was extravasated in one case (Case 1) that went on to develop Grade III AEs. In two other cases (Cases 9 and 12), an estimated 25% of doxorubicin was extravasated, both treated with dexrazoxane; one developed Grade II and the other developed Grade III AEs. An estimated 25% of vincristine was extravasated in one case (Case 22) which resulted in Grade III AE. This case did not receive a neutralizing agent. It was estimated that less than 5% of drug was extravasated in two cases (Cases 6 and 10) receiving doxorubicin (both resulting in Grade II AEs after treatment with dexrazoxane) and one case (Case 16) receiving mitoxantrone (resulting in Grade 0 AE). Eighteen EEs occurred at a specialty hospital (five at an academic facility and 13 at a specialty private practice) and five occurred at a primary care facility. Of those occurring at a primary care facility, there were three doxorubicin EEs (one each of Grades III–V) and two vincristine EEs (both Grade III). Of the EEs occurring in the specialty hospital setting, all cases were administered chemotherapy by two individuals (either two veterinary technicians or one veterinary technician and one veterinary specialist) except one case (Case 8) which was administered chemotherapy by a veterinary technician and a primary care veterinarian employed by the specialty hospital. Reporting on the skill level of those administering chemotherapy in the five EEs occurring in the primary care setting was not available.

3.3 | Extravasation Treatments (ETs)

ETs employed and grade of extravasation AEs for each case are summarized on Table S2. Treatments included attempts to aspirate back extravasated drug, use of warm and/or cold compress, use of neutralizing agents such as dimethyl sulfoxide (DMSO), dexrazoxane, or hyaluronidase, use of supportive oral, injectable, or topical medications, use of bandages, surgical interventions, and inpatient or outpatient treatment. Attempts to aspirate extravasated drug occurred in a total of eight cases ($n = 4$ doxorubicin, $n = 2$ mitoxantrone, $n = 1$ rabacfosadine, $n = 1$ vincristine). These cases had extravasation AEs ranging from Grades 0 to III; however, other cases with the same drug extravasated in which aspiration was not performed also experienced AEs of similar grades. Cold compresses were used in all cases of doxorubicin ($n = 9$), mitoxantrone ($n = 2$), and dacarbazine ($n = 1$) extravasation, and in two cases of carboplatin extravasation. Warm and cold compresses were alternated in EE from carboplatin ($n = 1$) and rabacfosadine ($n = 1$). Warm compresses were used in EE from vincristine ($n = 1$) and vinorelbine ($n = 1$). No compresses were used in EE from carboplatin ($n = 2$), vincristine ($n = 2$), and vinblastine ($n = 1$). The neutralizing agent dexrazoxane was used in all but one case of doxorubicin EE ($n = 8/9$). Dexrazoxane was administered at a median dose of 287 mg/m^2 (range 217–373 mg/m^2 IV) within the first 2 h, then at 24 and 48 h after the EE in six cases (includes Cases 6, 7, 9, 11, 13, 14, as designated on Table S2). Case 8 received 300 mg/m^2 dexrazoxane IV within 1 h of EE, then again once 36 h later. Case 10 received 300 mg/m^2 dexrazoxane IV once within 1 h of EE only. The cases receiving dexrazoxane had extravasation AEs ranging from Grades 0 to V, while the one case that did not receive dexrazoxane (Case 12) had extravasation AE Grade III. The neutralizing agent DMSO was used in two cases (Cases 9 and 11) of doxorubicin EE, and one case each of dacarbazine (Case 15) and mitoxantrone (Case 16) EE. Frequency of DMSO use was variable.

Hyaluronidase was used in one case each of vincristine (Case 22) and vinorelbine (Case 23) EE. In both cases, hyaluronidase was administered as 300 units diluted in 3–6 mL of 0.9% sterile sodium chloride and then subcutaneously injected circumferentially around the extravasation site.

Oral supportive medications included antibiotics (cefalexin, cefovecin, marbofloxacin, enrofloxacin, amoxicillin/clavulanic acid, chloramphenicol), antihistamines (diphenhydramine), nonsteroidal anti-inflammatory drugs (carprofen, meloxicam), prednisolone, and pain medications (gabapentin, buprenorphine). Injectable supportive medications included antibiotics (enrofloxacin, amoxicillin/clavulanic acid), diphenhydramine, dexamethasone, and pain medications (fentanyl, methadone, hydromorphone). Topical supportive therapies included hydrocortisone cream, antibiotics (neomycin-polymyxin B-bacitracin, silver sulfadiazine), wound dressing (calcium alginate, manuka honey), antifungal-antibiotic-steroid cream (nystatin, neomycin sulfate, thiostrepton, and triamcinolone acetonide [Animax]). The use of supportive therapies was case and clinician dependent; therefore, it was highly variable.

Bandages were used in eight cases ($n=4$ carboplatin, $n=3$ doxorubicin, $n=1$ rabacfosadine). The majority of cases had wet-to-dry bandages placed. Case 11 had a vacuum-assisted closure after doxorubicin extravasation, before amputation. All cases of carboplatin ($n=5$) and two cases of doxorubicin (Cases 7 and 11) extravasation required surgical debridement of the wound. One case with doxorubicin EE (Case 9) received inpatient care not due to medical necessity, rather for convenience due to serial administration of dexrazoxane. Three of the five carboplatin EE cases (Cases 1–3) and two doxorubicin EE cases (Cases 7 and 11) required inpatient treatment. In both doxorubicin cases, amputation was ultimately recommended despite surgical debridement. Case 7 was euthanized at the time amputation was recommended. This latter case was the only Grade V AE in this study.

3.4 | Adverse Events

Carboplatin EE resulted in Grade III ($n=4/5$) and Grade IV ($n=1/5$) AEs. All cases experiencing carboplatin extravasation required surgical debridement, and three of the five cases required inpatient management. Doxorubicin EE resulted in Grade 0 ($n=2/9$), Grade II ($n=4/9$), and one each of Grades III–V AEs. Three cases required inpatient management, two (Cases 7 and 11) due to the management of the wound, and one (Case 9) due to convenience for the administration of dexrazoxane. Extravasation of vinca alkaloids (vinblastine, vincristine, vinorelbine) resulted in Grade II ($n=3/5$) and Grade III ($n=2/5$) AEs, all of which were managed in the outpatient setting. Mitoxantrone and dacarbazine EE resulted in Grade 0 AEs for all cases ($n=2$ mitoxantrone and $n=1$ dacarbazine). Rabacfosadine EE resulted in Grade III AE, which was managed in the outpatient setting.

Nineteen cases experienced short-term AEs described as including one or more of the following clinical signs: erythema, bruising, edema, ulceration, eschar formation, necrosis, pain, lameness on the affected limb, focal wound pruritus, cellulitis, purulent discharge, and/or infection (Figures S1–S3a). Four cases ($n=2$ doxorubicin, Cases 8 and 13) and ($n=2$ mitoxantrone, Cases 16 and 17) did not experience short-term AEs. Six cases ($n=2$ carboplatin, Cases 1 and 4; $n=3$ doxorubicin, Cases 6, 9, and 12; $n=1$ vincristine, Case 22) experienced long-term AEs described as including one or more of the following clinical signs: alopecia, scar formation. Case 9 also developed an ulcerated wound approximately 64 days after the EE, despite evidence that the extravasation injury was fully healed by Day 28 post-EE. The ulcerated wound in this case took approximately 1 month to heal by second intention (Figure S3a–d). The duration of short- and long-term AEs was not reported in most cases. Amputation was recommended in two cases of doxorubicin EE (Cases 7 and 11) due to the extent of the extravasation injury; Case 11 received amputation while Case 7 was euthanized.

3.5 | Outcomes Section

Two cases (Cases 4 and 5) discontinued chemotherapy due to their carboplatin EE, one case (Case 7) discontinued chemotherapy due to client decision for euthanasia instead of amputation after doxorubicin EE, five cases ($n=3$ vinca alkaloid, Cases 21, 22, and 23; $n=1$ mitoxantrone, Case 16; $n=1$ rabacfosadine, Case 18) discontinued chemotherapy after EE for unknown reasons, and 15 cases continued chemotherapy after EE. Fourteen cases were reported dead, 12 due to progressive neoplasia and two due to causes unrelated to neoplasia or EE. Five cases were lost to follow-up, three cases were alive, and one case (Case 7) was euthanized due to EE.

4 | Discussion

This is a descriptive study of chemotherapy extravasation injuries in dogs and cats. Doxorubicin was the most common extravasated drug in this study, likely a result of reporting bias given the known severity of extravasation injury with this drug. Carboplatin was the second most common extravasated drug in this study. We suspect that extravasation of other drugs that result in less severe or absent clinical signs was underreported.

Doxorubicin EE resulted in Grade 0 ($n=2/9$), Grade II ($n=4/9$), and one each of Grades III–V AEs. The doxorubicin was diluted in all but one case (Case 9, Grade II AE). The cases with the most severe AEs (Case 11, Grade IV and Case 7, Grade V) were estimated to have 100% of the drug volume extravasated, while cases reported to have 25% or less drug extravasated experienced only mild–moderate AEs (Grades II–III), suggesting that the volume of drug extravasated might play an important role in the severity of doxorubicin extravasation injuries. To our knowledge, this has not been previously evaluated as a risk factor for extravasation injury in veterinary medicine. Studies evaluating a larger population are needed to explore this further. All but one doxorubicin EE case ($n=8/9$) received the neutralizing agent dexrazoxane. Cases receiving dexrazoxane experienced AEs ranging from mild to severe (Grades 0–V). The one case in which dexrazoxane was not used (Case 12) developed Grade III AEs. Given the variability of the dose, timing, and frequency of dexrazoxane in this study, strong conclusions on the overall benefit of dexrazoxane and the impact of dose, timing, and frequency of this neutralizing agent in dogs and cats experiencing doxorubicin EE cannot be made. Dexrazoxane is FDA-approved for the treatment of anthracycline extravasation in humans [14, 15]. At the time of this writing, one case series and a few case reports have been published on the use of dexrazoxane for the treatment of doxorubicin extravasation in dogs or cats [9–11]. Venable et al. described three of four dogs with doxorubicin EE that received dexrazoxane between 1 and

3 h post-EE. The fourth dog did not receive dexrazoxane until 48 h after EE when clinical signs of extravasation injury were reported [9]. This latter dog had the only case in this series that required amputation [9]. In the present study, the doxorubicin EE cases with the most severe AEs requiring amputation (Cases 7 and 11) both received dexrazoxane within 2 h of the EE; therefore, it is less likely that the timing of dexrazoxane administration played a role here. Further studies to evaluate the optimal dexrazoxane dose, timing, and frequency in dogs and cats experiencing doxorubicin extravasation are needed. The majority of cases experiencing doxorubicin EE (6/9) were managed on an outpatient basis. Three of nine cases were managed as inpatients, 2/3 due to the severity of extravasation injury (Case 7 and 11), and 1/3 due to client convenience during serial administration of dexrazoxane.

This study found that carboplatin was the second most common extravasated drug and that all five cases experiencing carboplatin EE resulted in Grade III or IV AEs which required surgical debridement. In one of the five cases, it was estimated that 75% of carboplatin was extravasated. This case (Case 1) experienced Grade III AEs. In the other four cases, the estimated volume of drug extravasated was unknown ($n = 3$ Grade III and $n = 1$ Grade IV). Given the small sample size, the effect of the volume of drug extravasated with respect to carboplatin EE is unknown. Historically, carboplatin has been thought to be an irritant rather than a vesicant [6, 16]. Intracavitary carboplatin for the treatment of neoplastic effusions is not associated with tissue injury [17]. In another study, subcutaneous carboplatin was administered via an indwelling subcutaneous catheter placed at the amputation site or the interscapular region in 17 dogs as adjuvant therapy for osteosarcoma [18]. This study concluded that the surgical infection rate was higher in these dogs compared with infection rates following clean surgeries [18]. The authors of this study concluded that it is unknown if the localized infusion of carboplatin at the surgical site contributed to the increased infection rate. In another study, carboplatin caused ulcerations when administered intradermally to laboratory mice at concentrations greater than or equal to 10 mg/mL [19]. Additionally, Miller et al. evaluated carboplatin extravasation in seven dogs, and although the extravasation injuries were not graded according to VCOG-CTACE criteria, six dogs developed full-thickness necrosis and had to receive surgical debridement [8]. Our study further demonstrates the potential for carboplatin to act as a vesicant. At this time, it is unknown what factors might contribute to the AEs from carboplatin extravasation. One possibility is that carboplatin can be diluted in 5% dextrose solution, which can contribute to irritation if extravasated; however, this is unlikely the causative factor in this study given that dilution did not occur in any of the carboplatin EE reported here [20]. Based on the findings in this study as well as prior studies, it is recommended to have a heightened awareness of the risks of extravasation injury when administering carboplatin [8, 18].

In this study, vinca alkaloid EE resulted in mild–moderate (Grades II–III) AEs. In physician-based medicine, hyaluronidase is recommended for the treatment of vinca alkaloid extravasations [21, 22]. Spugnini et al. evaluated the use of hyaluronidase for the treatment of extravasation of vincristine ± mechlorethamine or doxorubicin in six dogs. In this study, the injections were repeated weekly until side effects resolved, and all dogs recovered within 6 weeks [12]. In the current study, there were five vinca alkaloid EE, and two (Cases 22 and 23) were treated once with hyaluronidase. The severity of AEs (Grades II–III) for these two cases was similar to the severity of AEs for the three cases not treated with hyaluronidase. Given the small sample size and only one-time use of this neutralizing agent compared to the Spugnini et al. study, strong conclusions on the effect of hyaluronidase on vinca alkaloid EE cannot be made in the current study.

In the current study, mitoxantrone EE ($n = 2$) and dacarbazine EE ($n = 1$) resulted in no AEs. One of the mitoxantrone EE (Case 17) was due to leakage of the chemotherapy agent into the subcutaneous space during intracavitary administration. While this does not fit the true definition of extravasation, this case was not excluded from this study, as some reports classify mitoxantrone as a vesicant that causes tissue damage based on concentration and volume [1, 5–7]. Rabacfosadine EE ($n = 1$) resulted in Grade III AEs and was managed in the outpatient setting. Larger studies are required to further explore the severity of AEs resulting from extravasation of these chemotherapy agents.

In physician-based medicine, cold compresses are recommended for extravasations of DNA binding agents, while warm compresses are recommended for extravasations of non-DNA binding agents [1, 21]. In the current study, given the small sample size and variability of use, the benefit of aspirating extravasated drug, compresses, and neutralizing agents is unknown. The use of supportive care and bandages was variable and dependent on individual case clinical factors and clinician preferences; thus, strong conclusions on the effect of these treatments cannot be made.

The majority of cases (20/23) had mild to moderate or no AEs associated with the EE. Three of the 23 cases had severe (Grade IV–V) AEs secondary to doxorubicin EE ($n = 2$, one Grade IV and one Grade V) and carboplatin ($n = 1$, Grade IV). Amputation was required for both latter cases of doxorubicin EE, one case of which the owners ultimately elected euthanasia instead of undergoing amputation.

The majority of EE occurred within the first four chemotherapy administrations (18/23, 78%), with extravasation occurring at the first chemotherapy administration in 7/23 (30%) of cases. Furthermore, 19 cases were fully awake and received no form of injectable or oral sedatives before chemotherapy administration. These factors highlight the need for careful consideration of the animal's compliance, especially early in the treatment protocol when personnel are naïve to how the animal will react to restraint and venipuncture. The use of chemical restraint could be considered to mitigate the potential for EE due to animal noncompliance. However, this is not a foolproof measure as one case in this study still experienced doxorubicin EE despite injectable sedation protocol.

The majority (18/23) EE occurred at a specialty hospital (academia or specialty private practice). Given that it is more common for chemotherapy to be administered in the specialty hospital setting in veterinary medicine, this finding is not

surprising. In addition, selection bias is likely a factor in this population, given that cases were recruited through a specialist online listserv.

In physician-based medicine, there are several reported risk factors for extravasation injuries, including but not limited to small veins, age, and use of large gauge catheters or butterfly catheters [3, 5–7]. In the current study, there were six cases weighing less than 7.5 kg, but in these, the extravasation injuries were overall mild (Grades 0–II). The catheter gauge used for the cases that reported the size was standard 22-gauge (8/23) and 25-gauge (2/23). A butterfly catheter was used in only one case, while the majority (21/23) had chemotherapy administered via intravenous catheter. Given the small sample size, it is difficult to determine how much of a role these risk factors played in the EE in this study. Fluid pump-assisted administration was used in one case of doxorubicin EE and one case of dacarbazine EE in this study. This method of delivery is discouraged when administering drugs with known extravasation risk to veterinary species, especially in instances in which the animal is not being closely monitored or restrained, as animal movement can cause the intravenous catheter to become displaced, and the fluid pump continues to push fluid regardless of catheter patency.

The left forelimb was the most common location for EE to occur (11/23 cases, 48%). The reason for this is likely multifactorial, including that the forelimbs might be more commonly used for chemotherapy administration due to accessibility, or perhaps restraint of the animal for venipuncture in this position is more likely to be compromised. As the majority of the human population is right-handed, it is possible that placing an intravenous catheter in the left front limb could be more technically challenging, potentially leading to errors in catheter placement. Given the small sample size of this population, it is difficult to draw strong conclusions.

The majority of cases experiencing EE did not experience severe AEs and were able to go on to complete chemotherapy. Only five cases experienced long-term AEs, including scar formation or alopecia. Two cases discontinued chemotherapy due to the EE, and one case discontinued chemotherapy due to the client decision for euthanasia instead of amputation after EE.

5 | Limitations

A major limitation of this study is its retrospective nature, including the assignment of AE grade. Reporting bias might also be at play given that extravasation of drugs known to cause severe injury or EEs that caused severe clinical signs were more likely reported. In addition, extravasation might not be recognized at the time it occurs and therefore not be well documented in medical records. Less severe AEs (Grades 0–I) might be underreported due to minimal clinical signs. Selection bias was introduced given that the contributors to this study are all oncology specialists, and the oncology specialty listserv was used to recruit cases. It is possible that more cases could have been obtained if the case search had been opened to general practitioners and internal medicine specialists. Furthermore, the small case numbers and variability in EEs and treatments preclude the possibility of strong conclusions.

6 | Conclusion

Chemotherapy extravasation is a potentially serious complication. This study demonstrated that doxorubicin and carboplatin extravasations caused the most serious AEs. Two cases in which it was estimated that the majority of doxorubicin was extravasated resulted in more serious complications. However, due to the small sample of cases in which the volume extravasated was reported, a strong conclusion on the impact of the volume extravasated on AE severity cannot be formed. This study supports handling carboplatin as a vesicant rather than an irritant. Personnel administering chemotherapy must be aware of the risks and complications from extravasation injury and make efforts to reduce the risk. This study demonstrated that the majority of extravasations occurred within the first four treatments and that nearly all cases were fully awake and received no sedation before treatment. The use of chemical restraint can be considered by care teams to help mitigate risks, especially in cases receiving chemotherapy known to cause severe extravasation injury, although this might not be appropriate for every case depending on other clinical factors.

Disclosure

Authors declare no off-label use of antimicrobials.

Ethics Statement

Authors declare no Institutional Animal Care and Use Committee or other approval was needed. All clients consented to the treatment provided to these animals. Authors declare human ethics approval was not needed.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. J. T. Kim, J. Y. Park, H. J. Lee, and Y. J. Cheon, "Guidelines for the Management of Extravasation," *Journal of Educational Evaluation for Health Professions* 17 (2020): 21.

2. S. W. Langer, "Extravasation of Chemotherapy," *Current Oncology Reports* 12, no. 4 (2010): 242–246.

3. J. Boulanger, A. Ducharme, A. Dufour, S. Fortier, and K. Almanric, "Management of the Extravasation of Anti-Neoplastic Agents," *Supportive Care in Cancer* 23, no. 5 (2015): 1459–1471.

4. C. F. Saba, T. M. Fan, B. S. Phillips, Z. M. Wright, and D. H. Thamm, "Alternating Rabacfosadine and Doxorubicin for Treatment of naïve Canine Lymphoma," *Veterinary and Comparative Oncology* 22, no. 2 (2024): 278–283.

5. Y. Wengström and A. Margulies, "European Oncology Nursing Society Extravasation Guidelines," *European Journal of Oncology Nursing* 12, no. 4 (2008): 357–361.

6. R. A. Ener, S. B. Meglathery, and M. Styler, "Extravasation of Systemic Hemato-Oncological Therapies," *Annals of Oncology* 15, no. 6 (2004): 858–862.

7. C. Sauerland, C. Engelking, R. Wickham, and D. Corbi, "Vesicant Extravasation Part I: Mechanisms, Pathogenesis, and Nursing Care to Reduce Risk," *Oncology Nursing Forum* 33, no. 6 (2006): 1134–1141.

8. K. B. Miller, A. Lejeune, R. Regan, A. Szivek, and K. Kow, "Suspected Carboplatin Extravasation Reactions in Seven Dogs," *Journal of the American Animal Hospital Association* 54, no. 6 (2018): 360–367.

9. R. O. Venable, C. F. Saba, M. M. Endicott, and N. C. Northrup, "Dexrazoxane Treatment of Doxorubicin Extravasation Injury in Four Dogs," *Journal of the American Veterinary Medical Association* 240, no. 3 (2012): 304–307.

10. K. S. Kicenuik, N. C. Northrup, D. M. Clarke, and L. J. Bazzle, "Successful Management of Doxorubicin Overdose and Extravasation in a Dog With Lymphoma," *Canadian Veterinary Journal* 59, no. 10 (2018): 1079–1084.

11. J. A. Mahoney, P. J. Bergman, M. A. Camps-Palau, and T. L. Hull, "Treatment of Doxorubicin Extravasation With Intravenous Dexrazoxane in a Cat," *Journal of Veterinary Internal Medicine* 21, no. 4 (2007): 872–873.

12. E. P. Spugnini, "Use of Hyaluronidase for the Treatment of Extravasation of Chemotherapeutic Agents in Six Dogs," *Journal of the American Veterinary Medical Association* 221, no. 10 (2002): 1437–1440.

13. A. K. LeBlanc, M. Atherton, R. T. Bentley, et al., "Veterinary Cooperative Oncology Group—Common Terminology Criteria for Adverse Events (VCOG-CTCAE v2) Following Investigational Therapy in Dogs and Cats," *Veterinary and Comparative Oncology* 19, no. 2 (2021): 311–352.

14. R. C. Kane, W. D. McGuinn, R. Dagher, R. Justice, and R. Pazdur, "Dexrazoxane (Totect™): FDA Review and Approval for the Treatment of Accidental Extravasation Following Intravenous Anthracycline Chemotherapy," *Oncologist* 13, no. 4 (2008): 445–450.

15. H. T. Mouridsen, S. W. Langer, J. Buter, et al., "Treatment of Anthracycline Extravasation With Savene (Dexrazoxane): Results From Two Prospective Clinical Multicentre Studies," *Annals of Oncology* 18, no. 3 (2007): 546–550.

16. B. Biller, J. Berg, L. Garrett, et al., "2016 AAHA Oncology Guidelines for Dogs and Cats," *Journal of the American Animal Hospital Association* 52, no. 4 (2016): 181–204.

17. S. C. Charney, P. J. Bergman, J. A. McKnight, et al., "Evaluation of Intracavitary Mitoxantrone and Carboplatin for Treatment of Carcinomatosis, Sarcomatosis and Mesothelioma, With or Without Malignant Effusions: A Retrospective Analysis of 12 Cases (1997–2002)," *Veterinary and Comparative Oncology* 3, no. 4 (2005): 171–181, https://doi.org/10.1111/j.1476-5810.2005.00075.x.

18. J. O. Simcock, S. S. Withers, C. Y. Prpich, C. A. Kuntz, and B. E. Rutland, "Evaluation of a Single Subcutaneous Infusion of Carboplatin as Adjuvant Chemotherapy for Dogs With Osteosarcoma: 17 Cases (2006–2010)," *Journal of the American Veterinary Medical Association* 241, no. 5 (2012): 608–614.

19. R. S. M. Marnocha and P. R. Hutson, "Intradermal Carboplatin and Ifosfamide Extravasation in the Mouse," *Cancer* 70, no. 4 (1992): 850–853.

20. Pfizer Carboplatin Package Insert, "Carboplatin Injection," accessed April, 2018, https://labeling.pfizer.com/ShowLabeling.aspx?id=4379.

21. L. Schulmeister, "Extravasation Management: Clinical Update," *Seminars in Oncology Nursing* 27, no. 1 (2011): 82–90.

22. G. Bertelli, D. Dini, G. B. Forno, et al., "Hyaluronidase as an Antidote to Extravasation of Vinca Alkaloids: Clinical Results," *Journal of Cancer Research and Clinical Oncology* 120, no. 8 (1994): 505–506.

Supporting Information

Additional supporting information can be found online in the Supporting Information section.