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Pharmacological management of anticancer agent extravasation: A single institutional guideline

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Abstract

Although the risk of extravasation of a chemotherapy (anticancer) medication is low, the complications associated with these events can have a significant impact on morbidity and health care costs. Institutions that administer anticancer agents should ideally have a current guideline on the proper management of the inadvertent administration of these toxic medications into tissues surrounding blood vessels. It is imperative that the health care team involved in administering drugs used to treat cancer be educated on the risk factors, preventative strategies and treatment of anticancer extravasations, as well as practice safe and proper administration techniques. Anticancer agents are generally divided into classes based on their ability to cause tissue damage. The review of current published guidelines and available literature reveals a lack of consensus on how these medications should be classified. In addition, many recently approved drugs for the treatment of cancer may lack data to support their classification and management of extravasation events. The treatment of the majority of extravasations of anticancer agents involves nonpharmacological measures, potentially in the ambulatory care setting. Antidotes are available for the extravasation of a minority of vesicant agents in order to mitigate tissue damage. Due to the limited data and lack of consensus in published guidelines, a working group was established to put forth an institutional guideline on the management of anticancer extravasations.

Keywords

Antineoplastic, anticancer, chemotherapy, extravasation, irritant, vesicant

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Introduction

Anticancer agents, which are commonly administered via the intravenous (IV) route, are generally separated into two broad categories based on their ability to cause tissue injury: vesicants or irritants. Vesicants are defined as agents that are capable of causing soft tissue damage by causing blistering and necrosis, while irritants cause inflammatory reactions.[1] Additionally, the European Oncology Nursing Society (EONS) describes a third category of intravenous medications, the nonvesicants.[2] Nonvesicants are agents that do not produce necrosis or inflammation.[3] Extravasation is the inadvertent administration of a vesicant solution from a vein, while infiltration refers to leakage of an irritant into the extravascular space.[1,2,4] Initial symptoms of extravasation and infiltration are clinically similar and include persistent pain, burning, stinging, swelling and either blanching or erythema at the site of injection or along the course of a vein. Unlike irritants, vesicant medications notably are capable of causing blistering, ulceration and tissue necrosis if administered outside of a vein. Such a clinical scenario may lead to death if left

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untreated and, therefore, may necessitate surgical debridement or skin grafting, possibly resulting in permanent patient disability and disfigurement.[4] Extravasation of an anticancer agent is potentially a medical emergency that requires prompt recognition and action to ensure patient safety. The term ''anticancer agents'' in this article describes classic cytotoxic chemotherapy agents as well as biotherapy.

Although the exact incidence is unknown due to the lack of a central reporting database, it is estimated that extravasation occurs at 0.1–6% for all cytotoxic drug administrations.[1,5,6] Some data suggest that the overall incidence is decreasing due to better recognition and training in management techniques.[2] In addition, the routine use of central venous administration could also contribute to the decreased incidence as central venous access devices (CVAD) are associated with decreased risk of extravasation.

Risk factors and prevention

There are a variety of risk factors associated with extravasation that can be separated into those associated with the clinician, patient, agent, and device (Table 1). Identification of potential risk factors prior to intravenous anticancer medication infusions will mitigate inadvertent administration of these medications into the extravascular space. In addition, oncology nurses should receive specialized education and training in order to appropriately administer chemotherapy and biotherapy, as well as to promptly recognize and manage extravasation injuries to ensure a safe level of care for individuals receiving these agents. Prevention is the ideal approach when potentially encountering anticancer extravasation injury. Strategies to prevent or minimize antineoplastic medication extravasation are listed in Table 1.

Management

Anticancer drug classification

Multiple organizations, including the European Society of Medical Oncology-European Oncology Nursing Society (ESMO-EONS) and the Oncology Nursing Society (ONS), have guidelines for management of chemotherapy extravasations.[2,5] However, there is a lack of consensus on the classification of intravenously administered anticancer drugs and their proper extravasation management. In an effort to construct an institutional guideline, a working group at the University of Illinois Hospital and Health Sciences System (UIHHS) was organized to review the current literature in order to classify and recommend optimal pharmacological extravasation strategies for select anticancer intravenous agents.

A review of the literature incorporating manufacturer package inserts, oncology nursing society guidelines and available patient case reports demonstrated wide variability distinguishing several intravenous anticancer medications based on tissue damage potential. Our PubMed and Google Scholar search terms

Table 1. Extravasation risk factors and prevention.[2,5–8]

	Risk factors	Prevention strategies
Clinician related	• Cannulation technique – untrained or inexperienced staff, multiple attempts at cannulation	• Educate all staff administering chemotherapies on risk identification, extravasation prevention and management, appropriate use of venous devices, and proper documentation
Patient related	• Age: >60 or ≤10 • Fragile veins • Compromised circulation ○ Severe peripheral vascular disease, lymphedema, superior vena cava syndrome, advanced diabetes, Raynaud syndrome	• Educate patients on risk of extravasation and instruct them to report any pain, burning, or change in sensation at injection site • Instruct patient not to reposition or remove cannula
Agent related	• pH <5 or >9 • High osmolality • Cytotoxicity–DNA binding more likely than non-DNA binding	• Preferred route of administration is via central IV access • Vesicant infusions lasting <60 min may be administered peripherally if observed during the entire infusion with IV patency confirmed every 5–10 min
Device related	• Metal needles • Large gage catheter (<18 gage) • Inadequately secured catheter • Location: dorsum of hand or wrist, antecubital fossa	• Use plastic cannulas • Use smallest gage feasible, 18 to 20 gage is preferred • Stabilize and secure needle with transparent dressing • Location: place cannula in forearm

included: extravasation, management, injury, chemotherapy, antineoplastic, cytotoxic, and individual drug and antidote names combined with Boolean operators. Papers describing surgical management of extravasation were excluded. In order to establish a classification scheme for our institution, we first examined how major nursing organizations describe the extravasation potential of commonly used anticancer agents. A summary of these anticancer drug classifications as either vesicants or irritants is compiled in Table 2. If guidance from ONS and EONS was conflicting, our working group made a conservative recommendation. Additionally, anticancer agents were initially limited to one of two categories, vesicants or irritants, as nonpharmacological management suggestions for ''nonvesicant'' extravasation were identical to those for irritants. In situations where EONS listed a medication as a nonvesicant, but was not identified by ONS as an irritant, the drug was placed into an irritant category, noting that particular medication ''may have irritant-like properties''. Additionally, both ONS and EONS state that some drugs listed as irritants may have vesicant-like properties or case studies describe them as capable of causing vesicant-like reactions. In this situation, these drugs were listed by the working group as irritants, with the caveat that patients may require additional monitoring. Often little, if any, published data or data from the drug manufacturers was available to guide classification for some of the more recently marketed yet frequently utilized agents in clinical practice (e.g. liposomal vincristine, romidepsin, carfilzomib). These medications were classified based on the most conservative information available. If an anti-cancer medication was not listed as either a vesicant or an irritant (Table 2) and did not have a specific antidote described in the literature, we consider their extravasation management similar to those for irritants unless otherwise specified. UIHHSS classification is summarized in Table 3.

The significant increase in the use of biotherapy in the oncology community over the past decade warranted inclusion of their extravasation management in our guideline. These agents do not generally produce irritation or tissue damage. However, due to our two category classification system we categorized monoclonal antibodies as anticancer drugs that may have irritant like properties. Conversely, antibody–drug conjugates (e.g. brentuximab and ado-trastuzumab) are complex molecules comprised of a monoclonal antibody attached to a cytotoxic component. Although there is minimal guidance and data to support classification and extravasation management, the cytotoxic moiety of these medications is an anti-microtubule, rendering them potentially capable of causing tissue necrosis. Therefore, these agents were classified as irritants that may have vesicant like properties. Neither of these antibody–drug conjugates is listed in ONS or EONS guidelines.

Additionally, with the exception of ixabepilone, the newer antimicrotubule agents, eribulin and cabazitaxel, are not included in either nursing guidelines and lack published evidence to accurately support classification. Eribulin and ixabepilone were classified as irritants that may have vesicant like properties as they are mechanistically similar to the taxanes and vinca alkaloids. The package insert for cabazitaxel does not identify this medication as an irritant or vesicant.[9] However, due to the structural and mechanistic similarity to docetaxel, the working group classified cabazitaxel as a vesicant.

General treatment measures

The vast majority of anticancer extravasations can be managed appropriately by initially utilizing nonpharmacological interventions as outlined in Figure 1, even for agents with a specific Food and Drug Administration (FDA) labeled antidote. Medication education is imperative for those receiving intravenous medications as self-reporting by patients can assist in early recognition of signs of extravasation. These listed measures should commence upon initial extravasation diagnosis as delaying proper treatment may result in significant patient injury. All members of the health care team caring for a patient receiving anti-cancer agents ideally should be knowledgeable of the extravasation guidelines for their institution. Also, access to an extravasation kit containing instructions, materials and medications is highly encouraged.[2]

There are several key elements of an extravasation event should be documented by nursing staff (Figure 2). The majority of irritant extravasations can be treated in the ambulatory setting with close follow up and patient education. Conversely, vesicant extravasation management may require hospitalization to allow for closer monitoring, additional treatment, and medical consultations as appropriate. Patient follow-up is dependent on host-specific factors, but at minimum should include periodic assessment as well as patient instruction to report fever, chills, blistering, skin sloughing, or worsening pain. Referral to specialized care (e.g. plastic surgery, physical therapy, or rehabilitation services) may be necessary.

Pharmacological interventions

For some extravasated anticancer agents, nonpharmacological management is insufficient. The goal of antidote administration is to reverse the action of the extravasated drug, interfere with the process of cell destruction, prevent tissue necrosis or limit the extent

Table 2. Drug classification by organization.[2,5,9,10]

Drug	ONS	EONS	UIHHSS
Ado-trastuzumab	Not listed	Not listed	May have vesicant-like properties
Arsenic trioxide	Not listed	Nonvesicant	May have irritant-like properties
Asparaginase	Not listed	Nonvesicant	May have irritant-like properties
Bendamustine	Irritant with vesicant-like properties	Vesicant	May have vesicant-like properties
Bleomycin	Nonvesicant	Irritant	Irritant
Bortezomib	Not listed	Nonvesicant	May have irritant-like properties
Brentuximab	Not listed	Not listed	May have vesicant-like properties
Cabazitaxel	Not listed	Not listed	Vesicant
Carboplatin	Irritant	Irritant	Irritant
Carfilzomib	Not listed	Not listed	May have irritant-like properties
Carmustine	Irritant	Irritant	May have vesicant-like properties
Cisplatin	Not listed	Irritant	Vesicant (>20 mL of >0.4 mg/mL) Irritant (if not >20 mL of >0.4 mg/mL)
Cladribine	Not listed	Nonvesicant	May have irritant-like properties
Cyclophosphamide	Not listed	Nonvesicant	May have irritant-like properties
Cytarabine	Not listed	Nonvesicant	May have irritant-like properties
Dacarbazine	Irritant	Irritant	Irritant
Dactinomycin	Vesicant	Vesicant	Vesicant
Daunorubicin	Vesicant	Vesicant	Vesicant
Docetaxel	Vesicant	Vesicant	Vesicant
Epirubicin	Vesicant	Vesicant	Vesicant
Eribulin	Not listed	Not listed	May have vesicant-like properties
Etoposide	Irritant	Irritant	Irritant
Etoposide phosphate	Not listed	Nonvesicant	Irritant
Fludarabine	Not listed	Nonvesicant	May have irritant-like properties
5-Fluorouracil	Not listed	Irritant	Irritant
Gemcitabine	Irritant	Nonvesicant	Irritant
Idarubicin	Vesicant	Vesicant	Vesicant
Ifosfamide	Irritant	Irritant	Irritant
Irinotecan	Irritant with vesicant-like properties	Irritant	May have vesicant-like properties
Ixabepilone	Not listed	Irritant	May have vesicant-like properties
Liposomal daunorubicin	Irritant	Irritant	Irritant
Liposomal doxorubicin	Irritant	Irritant	Irritant
Liposomal irinotecan	Not listed	Not listed	Irritant
Liposomal vincristine	Not listed	Not listed	May have vesicant-like properties
Mechlorethamine	Vesicant	Vesicant	Vesicant
Melphalan	Irritant with vesicant-like properties	Irritant	May have vesicant-like properties
Methotrexate	Not listed	Nonvesicant	May have irritant-like properties
Mitomycin	Vesicant	Vesicant	Vesicant
Mitoxantrone	Vesicant	Vesicant	Vesicant
Monoclonal antibodies	Not listed	Nonvesicant	May have irritant-like properties
Nab-paclitaxel	Vesicant	Not listed	Vesicant
Nelarabine	Not listed	Not listed	May have irritant-like properties
Omacetaxine	Not listed	Not listed	May have irritant-like properties
Oxaliplatin	Irritant with vesicant-like properties	Irritant	May have vesicant-like properties
Paclitaxel	Vesicant	Vesicant	Vesicant
Pemetrexed	Not listed	Nonvesicant	May have irritant-like properties

(continued)

Table 2. Continued

Drug	ONS	EONS	UIHHSS
Pentostatin	Not listed	Not listed	May have irritant-like properties
Pralatrexate	Not listed	Not listed	May have irritant-like properties
Romidepsin	Not listed	Not listed	May have irritant-like properties
Streptozocin	Irritant	Irritant	Irritant
Temsirolimus	Not listed	Nonvesicant	May have irritant-like properties
Teniposide	Irritant	Not listed	Irritant
Thiotepa	Not listed	Nonvesicant	May have irritant-like properties
Topotecan	Irritant	Irritant	Irritant
Trabectedin	Not listed	Not listed	Vesicant
Vinblastine	Vesicant	Vesicant	Vesicant
Vincristine	Vesicant	Vesicant	Vesicant
Vinorelbine	Vesicant	Vesicant	Vesicant

Table 3. Classification of vesicants versus irritants.

Vesicants	Cabazitaxel[9]		Meclorethamine[2,5]
	Cisplatin (>20 mL of >0.4 mg/mL)[11]		Mitomycin[2,5]
	Dactinomycin[2,5]		Mitoxantrone[2,5]
	Daunorubicin[2,5]		Nab-paclitaxel[5]
	Docetaxel[2,5]		Paclitaxel[2,5]
	Doxorubicin[2,5]		Trabectedin[10]
	Epirubicin[2,5]		Vinblastine[2,5]
	Idarubicin[2,5]		Vincristine[2,5]
			Vinorelbine[2,5]
Irritants	Ado-trastuzumab[a,12]	Dacarbazine[2,5]	Methotrexate[b,2]
	Arsenic trioxide[b,2]	Eribulin[a,2,5]	Monoclonal antibodies[b,2]
	Asparaginase[b,2]	Etoposide[2,5]	Nelarabine[b,13]
	Bendamustine[a,2,5]	Etoposide phosphate[2]	Omecetaxine[14]
	Bleomycin[2,5]	Fludarabine[b,2]	Oxaliplatin[a,2,5]
	Bortezomib[b,2]	5-Fluorouracil[2]	Pemetrexed[b,2]
	Brentuximab[15]	Gemcitabine[2,5]	Pentostatin[16]
	Carboplatin[2,5]	Ifosfamide[2,5]	Pralatrexate[b,17]
	Carfilzomib[18]	Irinotecan[a,2,5]	Romidepsin[b,19]
	Carmustine (BCNU)[a,2,5,20]	Ixabepilone[2]	Streptozocin[2,5]
	Cisplatin[2,11]	Liposomal daunorubicin[2,5,21]	Temsirolimus[b,2]
	Cladribine[b,2]	Liposomal doxorubicin[2,5]	Teniposide[5]
	Clofarabine[2]	Liposomal irinotecan[a,b,22]	Thiotepa[b,2]
	Cyclophosphamide[b,2]	Liposomal vincristine[23]	Topotecan[2,5]
	Cytarabine[b,2]	Melphalan[a,2,5]	

[a]May have vesicant-like properties. Additional monitoring may be required.
[b]May have irritant-like properties.

of tissue damage.[5] With the exception of dexrazoxane, which has been evaluated in single arm studies, the efficacy of extravasation antidotes has been evaluated primarily from animal studies or reported anecdotally based on human experience; therefore, their true efficacy is largely unknown.[1,2,4] Examples of medications used in the treatment of vesicant extravasation and their administration details are summarized in Table 4. In addition to the differences seen in drug classification, there are also a variety of recommended

1. Stop the infusion immediately.
2. Disconnect the IV tubing from the IV device. Do not remove the IV device or non-coring port needle.
3. Attempt to aspirate residual vesicant from the IV device or port needle using 1 -3 mL syringe.
4. Remove the peripheral device or port needle.
5. Assess the site of extravasation.
6. Assess the symptoms of the patient.
7. Notify the physician.
8. Apply warm (vinca alkaloids) or cold (all other anticancer medications) compress for 20 minutes 3 – 4 times daily for the first 24 – 48 hours after drug extravasation occurs.
9. Initiate proper pharmacologic management if indicated.

Figure 1. Initial management of extravasations.[2,5]

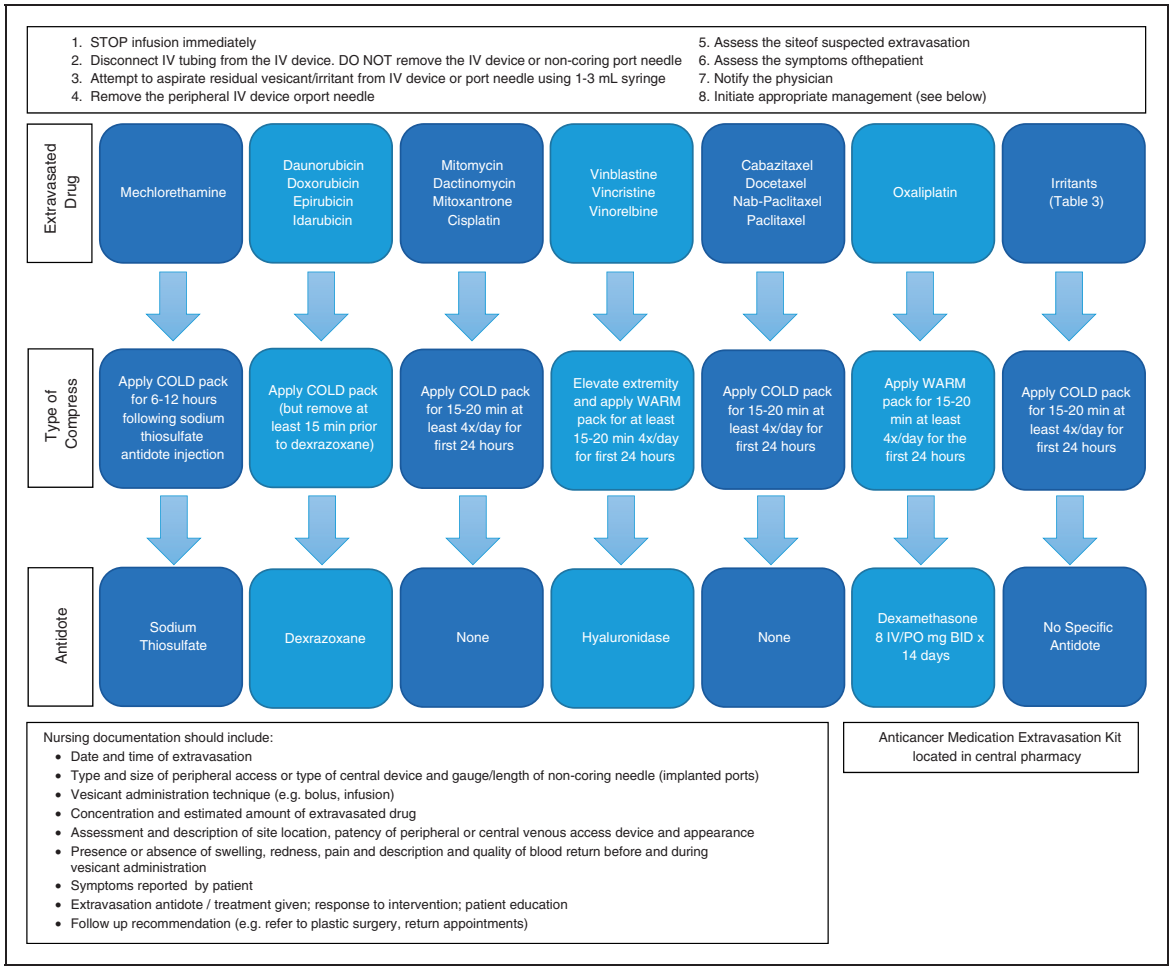

Figure 2. Extravasation management algorithm at University of Illinois Hospital and Health Sciences System.[2,5]

anticancer extravasation management steps in the literature. Drug shortages have created serious challenges in the oncology setting due to the lack of comparable alternatives for most agents. Although at the time of publication none of the antidotes listed in our algorithm are currently listed on the FDA Drug Shortage Index, some of these medications have been at one point in the past. The administration of these agents following an extravasation event is extremely time sensitive, necessitating an adequate stock of

Table 4. Antidotes used in chemotherapy extravasations.[1,2,4,5,24,29,33,36,39,43,45]

Antidote	Preparation	Administration
Dexrazoxane[a]	• Each vial of dexrazoxane 250 mg or 500 mg must be reconstituted with the supplied diluent (0.167 M sodium lactate injection) to a final concentration of 10 mg/mL • Dilute reconstituted solution in D5W or NS to a final concentration of 1.3–5 mg/mL	• Withhold cold pack 15 min prior to infusion • Begin infusion as soon as possible and within 6 h of anthracycline extravasation • Dose is based on patient's body surface area ○ Day 1: 1000 mg/m^2(max dose 2000 mg) ○ Day 2: 1000 mg/m^2 (max dose 2000 mg) ○ Day 3: 500 mg/m^2 (max dose 1000 mg)
Zinecard (Dexrazoxane)	• Available as 250 mg or 500 mg powder for injection to be reconstituted with sterile water for injection to a concentration of 10 mg/mL • Dilute reconstituted solution in lactated Ringer's to a final concentration of 1.3–3 mg/mL	• Treatment on day 2 and day 3 should start at the same hour (± 3 hours) as on day 1 • Reduce dose by 50% in patients with creatinine clearance <40 mL/min • Administer over 1 to 2 h in a large vein in an area remote from the extravasation • DMSO should not be used as it may diminish dexrazoxane efficacy
Hyaluronidase	• Vial contains 150 units per 1 mL or 200 units per 1 mL depending on manufacturer • To obtain a 15 unit/mL concentration, mix 0.1 mL (of 150 units/mL) with 0.9 mL normal saline in 1 mL syringe	• Inject 15–150 units of the hyaluronidase solution as five separate injections, each containing 0.2–1 mL of hyaluronidase • Use a 25-gage needle (change needle with each injection)
Sodium thiosulfate	• Prepare 1/6 molar solution: ○ From 25% sodium thiosulfate solution: mix 1.6 mL with 8.4 mL sterile water for injection ○ From 10% sodium thiosulfate solution: mix 4 mL with 6 mL sterile water for injection	• Use 2 mL of the prepared solution for each 1 mg drug extravasated • Inject SC using a 25-gage needle to affected area (change needle with each injection)

D5W: dextrose 5% water; IV: intravenous; NS: normal saline; SC: subcutaneous.
[a]Totect™ (Dexrazoxane) unavailable at the time this document was written.

these antidotes for institutions administering anticancer agents. The policy at our establishment is to perform periodic checks to ensure a sufficient supply of medications and that our policy and procedures are updated at a minimum every 2 years. In the event that an extravasation event occurs and the recommended antidote is not available, this step in management would be omitted. For the purpose of our institutional guideline, the working group opted to establish recommendations in line with the Oncology Nursing Society. Figure 2 represents the diagram based on our institutional guideline at the University of Illinois Hospital and Health Sciences System.

Dexrazoxane. Dexrazoxane is FDA approved for both the prevention of doxorubicin cardiomyopathy and the treatment of anthracycline extravasation. Anthracyclines are cytotoxic agents, which exert their cell killing by inhibition of topoisomerase II.[24] Dexrazoxane, a topoisomerase II catalytic inhibitor, antagonizes anthracyclines, and reduces oxidative stress, thereby protecting tissue from cytoxicity.[8,25–27] In animal studies, dexrazoxane was shown to significantly reduce the incidence of wound formation and duration of wound healing time when administered within 3 h of subcutaneous administration of an anthracycline (daunorubicin, doxorubicin, or idarubicin).[28] Two multicenter, single-arm studies, TT01 and TT02, evaluated the efficacy of intravenous dexrazoxane administration following accidental anthracycline administration.[29] The dose and schedule of dexrazoxane selected was based on previous animal studies that showed both a dose and schedule dependent effect. Patients received dexrazoxane at doses of 1000 mg/m^2 within 6 h of extravasation, followed by 1000 mg/m^2 and 500 mg/m^2 at 24 and 48 h respectively given in the opposite arm that the extravasation occurred. Results demonstrated that in 53 of 54 patients evaluated for efficacy, systemic dexrazoxane administration prevented surgery-requiring necrosis, as only 1 (2%) patient required surgical debridement. Local cooling was permitted in this study, but not within 15 min of dexrazoxane administration. In general, dexrazoxane is well tolerated with the most common adverse events being myelosuppression, transaminitis, nausea, and pain at the injection site. It should be noted that patients with reduced renal function (<40 mL/min) should receive 50% of the recommended dose and

that topical dimethyl sulfoxide (DMSO) should not be applied to patients receiving dexrazoxane as it may diminish dexrazoxane efficacy.[30,31] DMSO was once the standard of care for anthracycline extravasations. Several older studies utilized 99% grade topically for this indication. Historically, our institution extrapolated this data and listed 50% DMSO as an antidote for extravasation of this class of drugs in our extravasation management guidelines prior to the FDA approval of Totect™ due to the unavailability of 99% grade DMSO for purchase. Although the literature supports the efficacy of dexrazoxane for anthracycline extravasations, DMSO may be a possible alternative if dexrazoxane is not available.[31]

Liposomal doxorubicin is listed as an irritant and is generally managed with supportive care; however, there is a case report of a patient who did experience extravasation requiring dexrazoxane. In this case, the patient received dexrazoxane 3 days following accidental extravasation of liposomal doxorubicin.[32] The patient was initially treated with supportive care using cold compresses, and discharged home. Three days later the patient presented with increasing pain and erythema in the area of the extravasated liposomal doxorubicin, but developed increasing pain and erythema 3 days later. She was treated with dexrazoxane once daily for three consecutive days (1000 mg/m^2 days 1 and 2 and 500 mg/m^2 on day 3). The patient did not develop skin lesions, and did not lose any function at the site of extravasation (IV access site in distal part of left arm and extended to the left axilla).

In 2007, the FDA approved Totect™ for the treatment of anthracycline extravasation. The sponsor at that time obtained a new U.S. patent for dexrazoxane, which had been previously FDA approved for the prevention of doxorubicin-associated cardiomyopathy.[30] For a period of time, Totect™ was available in a kit for extravasation emergencies. However, since 2012 the product has been on long-term manufacturer backorder as the product was purchased by a new company. Two dexrazoxane products are currently available: Zinecard™, which is labeled for cardiomyopathy prevention, and generic dexrazoxane.[33] It is important to note that while these products are similar, they require unique methods of preparation (Table 4). Pricing between the two available products is similar (approximately US$500 per 500 mg vial).[34] According to the most recent Centers for Medicare & Medicaid Services (CMS) reimbursement codes, only one J-code is listed for dexrazoxane.[35] Therefore, CMS does not specify which product must be used for anthracycline extravasation in order to ensure reimbursement. Our institution currently keeps generic dexrazoxane in stock for this purpose.

Sodium thiosulfate. The recommendation for use of sodium thiosulfate to neutralize nitrogen mustards is largely based on the animal data.[36] In one study, intradermal sodium thiosulfate administration was shown to significantly reduce skin toxicity in mice following mechlorethamine extravasation. Little clinical data exist to support the benefit of sodium thiosulfate in humans. One case report describes the accidental intramuscular administration of mechlorethamine.[37] The patient received five separate 5 mL 1/6 M intramuscular injections of sodium thiosulfate surrounding the mechlorethamine injection site. During the subsequent weeks following accidental intramuscular injection, the patient did not experience any tissue destruction or ulceration.

Sodium thiosulfate is thought to chemically neutralize reactive mechlorethamine-alkylating species and reduce the formation of hydroxyl radicals, which can cause tissue injury.[36] Sodium thiosulfate should be administered subcutaneously immediately following extravasation using a 25-gage or smaller needle.[2] For each 1 mg of extravasated drug, 2 mL of the prepared solution should be administered. Administration may cause some local injection site reactions.

Sodium thiosulfate administration has also been reported in extravasation of other agents although neither ONS nor EONS recommends its use as an antidote for agents other than mechlorethamine. One study evaluated patients with extravasation of various agents (doxorubicin, epirubicin, vinblastine, and mitomycin C).[38] Patients were separated into two groups. One group received hydrocortisone and dexamethasone, while the other group received the same combination plus sodium thiosulfate. The mean healing time in the group who received sodium thiosulfate was about half that of the patients who did not receive sodium thiosulfate. However, this was a small, nonrandomized study.

Hyaluronidase. Hyaluronidase is an enzyme that degrades hyaluronic acid which is thought to improve the absorption of extravasated drugs.[2] There is evidence to support hyaluronidase in the extravasation of vinca alkaloids. Bertelli et al.[39] report a study of six patients who received vinca alkaloids and experienced extravasation. Patients were administered 250 units of hyaluronidase diluted in 6 mL normal saline subcutaneously as six injections around the extravasation area. These patients received hyaluronidase within 10 min of administration of the vinca alkaloids, resulting in the resolution of pain and symptoms in all patients within a few days. There was also one patient who was successfully treated 10 days after vinorelbine treatment with apparent extravasation.

There is conflicting data regarding the use of hyaluronidase for extravasation of paclitaxel, and therefore,

the practice is generally not recommended.[40] Hyaluronidase was originally tested for paclitaxel extravasations in a mouse model by Dorr et al.,[41] who found that intradermal hyaluronidase was more protective than saline for mice injected with high doses of intradermal paclitaxel. Dorr et al. concluded that 150 units hyaluronidase diluted in 3 mL saline may be beneficial for paclitaxel extravasations in humans. However, a study by Dubois et al.[42] found that patients who had extravasations of paclitaxel and were treated with hyaluronidase had longer recovery times than patients who did not receive hyaluronidase. Hyaluronidase does have an FDA indication to be used to increase the dispersion and absorption of other injected drugs, in a dose of 50–300 units.[43] Both EONS and ONS recommend the use of hyaluronidase following vinca alkaloid extravasation as 1 mL administered as five different subcutaneous injections surrounding the site of extravasation in a pentagon formation.[2,5] The most common adverse event associated with hyaluronidase is local injection site reaction.

Dexamethasone. In general, corticosteroids (topical or systemic) are not recommended for the management of anticancer extravasations, particularly extravasation of vinca alkaloids, as animal studies have demonstrated an increased area of skin necrosis.[44] However, intravenous or oral dexamethasone 8 mg twice daily for up to 14 days appears to have positive impact on oxaliplatin extravasation-related inflammation.[45]

Conclusion

To ensure patient safety every institution should have a current anticancer extravasation guideline in place. Although the risk of extravasation of intravenous anticancer medications is low due to increased use of central venous catheters in the United States, the health care team caring for patients receiving anticancer agents needs access to an institutional protocol in the event of this adverse outcome. Currently, national organizations with published anticancer medication extravasation management guidelines are oncology nursing societies. Neither national cancer medical organizations such as the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN) nor any pharmacy organizations have made statements on how to handle these oncological emergencies. Therefore, the stage is set for oncology pharmacists to contribute their unique expertise to the care of cancer patients and policy development of managing extravasations of these high-risk medications through proper classification in the setting of limited data and lack of uniformity in currently available guidelines.

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