

Overview, prevention and management of chemotherapy extravasation

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Abstract

Chemotherapy extravasation remains an accidental complication of chemotherapy administration and may result in serious damage to patients. We review in this article the clinical aspects of chemotherapy extravasation and latest advances in definitions, classification, prevention, management and guidelines. We review the grading of extravasation and tissue damage according to various chemotherapeutic drugs and present an update on treatment and new antidotes including dexrazoxane for anthracyclines extravasation. We highlight the importance of education and training of the oncology team for prevention and prompt pharmacological and non-pharmacological management and stress the availability of new antidotes like dexrazoxane wherever anthracyclines are being infused.

Key words: Chemotherapy; Extravasation; Vesicant; Tissue damage; Dimethyl sulfoxide; Dexrazoxane; Antidote; Hyaluronidase

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Core tip: Chemotherapy administration carries safety concerns, which include accidental extravasation, to patients. We review and update readers and health care providers on the risks of chemotherapy extravasation, prevention and management. We present the definitions, grading, classification and guidelines related to chemotherapeutic drugs and groups. We present an update on prevention and management and antidotes, particularly dexrazoxane for anthracyclines extravasation. We present summary statements of American Society of Clinical Oncology, European Society of medical Oncology, Oncology Nursing Society and European Oncology Nursing Society guidelines. We stress the importance of education and training of the entire oncology team members who share responsibility to ensure the safe

administration of chemotherapy and avoid extravasation.

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INTRODUCTION

Intravenous infusion is the principal modality of administration of anti-cancer drugs for most types of malignant disorders with numbers exceeding 1 million infusions each day worldwide^[1]. Chemotherapy administration carries safety concerns to both patients and the medical team. These concerns include extravasation of chemotherapy, which is defined as the accidental infiltration of chemotherapy into the subcutaneous or sub-dermal tissue at the injection site^[1-4], and can result in tissue necrosis^[1,2,4,5]. The exact incidence of chemotherapy extravasation varies greatly due to the general lack of reporting and absence of centralized registry of chemotherapy extravasation events. While center-based guidelines and policies attempt to minimize its risk, chemotherapy extravasation still has a prevalence that can range from 0.1% to 6% when administered through a peripheral intravenous access^[3] and from 0.26% to 4.7% when administered through a central venous access device (CVAD)^[6-8]. Institution-based guidelines should be based on evidence, where available, but they are often vague and non-specific, if present^[1,4].

In order to avoid additional chemotherapy adverse effects, every effort should be made to minimize the complications of chemotherapy administration. All the oncology team members share responsibility to ensure the safe administration of chemotherapy. In this article, we review the literature, provide clinical information on chemotherapy extravasation, and discuss guidelines and recommendations for its prevention and management. This article serves as a review of the clinical aspects of chemotherapy extravasation and latest advances in classification, prevention and management of chemotherapy extravasation.

This review includes a comprehensive literature search in the PubMed, Med-Line and Google Scholar databases was conducted for guidelines, case reports, clinical trials, retrospective studies and conferences on chemotherapy extravasation prevention and management. We used the following Medical Subject Headings terms: "Chemotherapy", "extravasation", "prevention", "management", "extravasation", and "guidelines" and combined them using boolean operators. Once we found a set of relative citations, we included citations using the "related articles" option as well. All references that we thought were relevant were printed and analyzed, and their main relevant ideas were paraphrased and noted. Literature review was focused on our research

question: "What should a healthcare practitioner know about chemotherapy extravasation, its prevention, and its management based on the current literature?"

CLASSIFICATION

Classification of intravenously administered drugs

Intravenously administered drugs can be classified into five categories according to their damage potential: Vesicant, Exfoliants, Irritants, Inflammittants, and Neutrals. The drug damage from extravasation can range from skin erythema to soft tissue necrosis. We list below examples of intravenously administered drugs according to various categories and in decreasing order of damage potential^[9-13].

Vesicants: Drugs that can result in tissue necrosis or formation of blisters when accidentally infused into tissue surrounding a vein^[14]. They include Actinomycin D, Dactinomycin, Daunorubicin, Doxorubicin, Epirubicin, Idarubicin, Mitomycin C, Vinblastine, Vindesine, Vincristine, and Vinorelbine.

Exfoliants (may have low vesicant potential):

Drugs that can cause inflammation and shedding (peeling off) of skin without causing underlying tissue death^[15]. Drugs may cause superficial tissue injury, blisters and desquamation^[12,13]. They include Aclacinomycin, Cisplatin, Docetaxel, Liposomal Doxorubicin, Mitoxantrone, Oxaliplatin, and Paclitaxel.

Irritants: Drugs that can cause inflammation, pain or irritation at the extravasation site^[14], without any blister formation. Clinicians use the term irritant also to refer to drugs that can cause a burning sensation in the vein while being administered: Bendamustine, bleomycin, carboplatin, dexrasoxane, etoposide, teniposide, and topotecan.

Inflammittants: Drugs that cause mild to moderate inflammation, painless skin erythema and elevation (flare reaction) at the extravasation site^[14]. They include bortezomib, 5-fluorouracil, methotrexate, and raltitrexed.

Neutrals: Drugs that neither cause inflammation nor damage upon extravasation^[14]. Monoclonal antibodies (rituximab and trastuzumab) are also listed under this category: Asparaginase, bevacizumab, bleomycin, bortezomib, cetuximab, cyclophosphamide, cytarabine, eribulin, fludarabine, gemcitabine, ifosfamide, melp-halan, rituximab, and trastuzumab.

Table 1 summarizes the different types of the above mentioned drugs according to their vesicant potential.

Vesicants may be sub-classified into DNA binding drugs and non-DNA binding drugs^[16]. DNA binding drugs are capable of producing more severe tissue damage and mainly include anthracyclines and alkylating agents such as mechlorethamine and bendamustine. Non-DNA

Table 1 The different types of the above mentioned drugs according to their vesicant potential

Neutrals	Inflammitants	Irritants	Exfoliants (may have low vesicant potential)	Vesicants
Asparaginase Bevacizumab bleomycin Bortezomib cetuximab, Cyclophosphamide Cytarabine eribulin Fludarabine gemcitabine Ifosfamide	Bortezomib 5-Fluorouracil methotrexate raltitrexed	Bendamustine Bleomycin	Aclacinomycin cisplatin Docetaxel liposomal Doxorubicin mitoxantrone Oxaliplatin paclitaxel	Actinomycin D Dactinomycin daunorubicin Doxorubicin epirubicin Idarubicin mitomycin C Vinblastine vindesine Vincristine vinorelbine
Melphalan rituximab Trastuzumab		Carboplatin dexrasoxane Etoposide Teniposide Topotecan		

binding compounds are mainly vinca alkaloids and taxanes^[13].

Drugs do not always fall under the strict definitions, and case reports of different extravasation potentials have been described. For example, taxanes have a poorly defined delineation between vesicants or irritants^[13]. Docetaxel, though usually referred to as an irritant, has exfoliant and low vesicant properties described in 12 case reports^[5,12,16-25]. While vinorelbine can cause severe irritation inside the vein site of infusion, it is a moderate vesicant if extravasated into the surrounding tissue^[17,18,25]. Alkylating agents like cyclophosphamide, ifosfamide and andmelphalan are considered neutrals^[16]. Although etoposide and teniposide are usually classified as irritants, they may have low vesicant potential if a highly concentrated infused drug is extravasated^[9].

Flare reaction, vessel irritation and venous shock, are other events that should be differentiated extravasation. Flare reaction is a not uncommon transient painless skin streaking erythema looking like urticaria with skin elevation that may occur with anthracycline administration. It is usually associated with itching, burning sensation and pain and that resolves within 1 to 2 h^[26,27]. Vessel irritation causes pain, discomfort and tightness along the infused vessel with possible accompanied erythema and dark skin discoloration^[27]. While both flare reaction and vessel irritation do not usually present with erythema, the extravasation is usually associated with swelling of the tissue surrounding the infused vein and predominantly manifests by erythema. The patient will complain of aches and burning sensation at the administration site. Unlike flare reaction and vessel irritation, extravasation is usually manifested with no or minimal blood return at the infusion site. Venous shock is due to the administration of very cold agents into the vein causing the loss of blood flow return due to venous muscle spasm, and it is managed by the application of warm compressors which can help to relax the vein^[27].

RISK FACTORS

Risk factors of chemotherapy extravasation

Risk factors are related to the chemotherapeutic

agent infused, patient factor, and iatrogenic causes. Factors related to chemotherapeutic agent itself and that increase the risk of chemotherapy extravasation include the vesicant properties of the drug, its concentration, volume and duration in which the infusion extravasated^[28]. Factors related to patients and that increase the risk of chemotherapy extravasation include small and/or fragile veins, lymphedema, obesity, impaired level of consciousness, and having had previous multiple venipunctures. Iatrogenic causes include lack of training of nurses, poor cannula size selection, poor location selection and lack of time. Extravasation can occur upon accidental puncturing of the vein or upon movement of the cannula itself due to movement of the patient or insecure fixing. Prolonged peripheral line infusions of vesicants carry an increased risk of extravasation and vesicants should not be infused as prolonged unsupervised infusions *via* a peripheral vein^[3].

CLINICAL MANIFESTATIONS

Tissue damage

Chemotherapy extravasation is manifested by a wide range of symptoms that can be mild and can present as an acute burning pain, swelling, at the infusion site. Symptoms vary according to the amount and concentration of extravasated drug. Pain and erythema, induration and skin discoloration progresses over few days and weeks, and may progress to blister formation. Blister formation or necrosis can lead to invasion and destruction of deeper structures^[1,3-5]. Damage can reach tendons, nerves, and joints^[19] depending on the location of the vein where extravasation occurs.

Grading of severity of extravasation

According to the latest Common Terminology Criteria for Adverse Events (CTCAE), published by the United States Department of Health and Human Services, National Institutes of Health, National Cancer Institute, and widely used in Clinical Trials^[20] (Version 4.0, May 2009), extravasation can be divided into four grades (Table 1) ranging from 2, which is manifested by erythema with associated edema, pain, induration, and phlebitis,

Table 2 Grades of Infusion site extravasation according to common terminology criteria for adverse events (V4.0, May 2009)

Adverse event	Grade				
	1	2	3	4	5
Infusion site extravasation	-	Erythema with associated symptoms (<i>e.g.</i> , edema, pain, induration, phlebitis)	Ulceration or necrosis; severe tissue damage; operative intervention indicated	Life-threatening consequences; urgent intervention indicated	Death

to grade 5, which refers to extravasation that leads to death. There is no grade 1. Table 2 shows the four grades of extravasation of chemotherapy (CTCAE V4).

Factors that determine the extent of tissue damage from chemotherapy extravasation

Factors that determine the extent of tissue damage from chemotherapy extravasation include its pH, osmolarity, vasoconstrictive potential, and duration for which it remains in tissue. Infusion solution whose pH is far from the physiologic pH (7.35-7.40) and/or osmolarity (281-282 mOsm/L) can irritate the venous endothelium and vessel wall and can damage the cell proteins and cause cell death^[21]. Hypertonic solutions can further increase tissue injury and lead to necrosis. Vesicants with high vasoconstrictive potential can result in tissue necrosis by severe vasoconstriction of capillary smooth muscles and reducing blood flow. Vesicants that are retained in extravasation tissue area for a long duration lead to a vicious cycle of direct cell injury. Typical examples are anthracyclines which enter the cells and bind to DNA causing immediate and continuous tissue injury. On the other hand, vesicants that are easily metabolized and are not retained in tissue include vinca alkaloids and taxanes. Despite their ability to cause direct tissue damage, they cannot bind to DNA and are easily metabolized^[21].

Manifestations of some commonly used chemotherapeutic drugs

Anthracyclines: Although all vesicants can cause tissue damage upon extravasation, anthracyclines, such as daunorubicin, doxorubicin, epirubicin, and idarubicin, have the greatest vesicant potential when compared to other chemotherapeutic agents. While all chemotherapeutic agents cause similar signs upon extravasation, anthracyclines are characterized by causing immediate pain and burning sensation, which can last up to hours and can be severe. Lesions form slowly over weeks and expand over periods of months due to tissue retention of the extravasant vesicant^[9]. Weeks after the extravasation episode, surrounding tissue may become red, firm and tender. The resolution of redness depends on the size of the extravasation area. If the area is small in size, redness will gradually resolve over the following weeks. If extravasation is significant, the center of the redness area becomes necrotic and painful. The accidental leak of anthracyclines can cause severe tissue damage. By cellular uptake and remaining for an extended period of time in tissue, they cause a continuous vicious cycle of tissue damage^[22-24,29]. In two

prospective, open-label clinical trials^[22,30], the patient with anthracycline extravasation who developed tissue necrosis had a large extravasation area of 253 cm². If the necrotic area is painful, surgical debridement may be required to remove any damaged and possibly infected necrotic tissue. In case no debridement is indicated, necrosis can progress to result in a thick, leathery eschar surrounded by a band of red painful skin, and can ulcerate to the underlying neurovascular tissue and tendons and cause pain. Ulceration is usually progressive and can result in persistent burning pain, nerve damage, and joint stiffness all of which may compromise the function of the involved organ or even cause its permanent disability^[29]. Spontaneous healing rarely occurs after anthracyclines extravasation. In addition to surgical debridement, split-thickness skin graft is usually required when the necrosis extends deep into the tissue. In case the periosteum of underlying bone was involved, the skin graft cannot survive on cortical bone and the area of injury should be covered instead by a pedicle skin flap^[23]. Dexrazoxane hydrochloride was FDA-approved for anthracyclines extravasation and has been reported to produce significant extravasation wound healing^[4].

Liposomal encapsulation of doxorubicin reduces the toxicity of doxorubicin extravasation by decreasing its diffusion capacity and hence its toxicity to healthy tissue^[31]. In phase II and III clinical trials assessing liposomal doxorubicin efficacy, two extravasations were reported and caused only inflammation with complete recovery and no tissue damage^[31]. In a few case reports of liposomal doxorubicin extravasation, patients had reported pain, erythema, and edema but no necrosis or ulceration of extravasation area nor there were need to undergo surgical debridement^[31].

Vinca alkaloids: Vinca alkaloids, which include vinblastine, vincristine, and vinorelbine, can cause direct cellular damage upon extravasation. Extravasation is known to cause a mostly painful ulceration, local paresthesia and slow healing^[9,32]. It can cause significant irritation and usually presents with intense pain around intravenous line or port site, erythema and tenderness^[32]. Erythema may be delayed by 1-2 h and even 3 d depending on the dosage of the vinca alkaloid administered^[32]. This is followed by blister formation, swelling and induration and can be complicated by sloughing, ulceration and tissue necrosis. Vinorelbine, which is a moderate vesicant, also causes common irritation and burning sensations which are prevented by proper dilution, short infusion time and use of an adequately large vein^[33].

Taxanes: Taxanes, including docetaxel and paclitaxel, are most often classified by literature as vesicants although there is no clear delineation. Most reactions following extravasation of taxanes consist of erythema, tenderness and swelling^[12]. There are case reports of patients who had necrosis and skin exfoliation^[34-38]. It is rare that taxane extravasation requires surgical debridement. In a paper that combined 35 case reports, only three patients developed ulceration two of whom required skin closure^[11].

Oxaliplatin: Platinum compounds have been classified as irritants. Oxaliplatin has been recently reported to have vesicant properties^[9]. Extravasation usually begins with a palpable swelling and discomfort upon palpation^[9]. Lesion usually progresses to erythematous painful lesions and resemble erysipelas^[9,10]. Long-term outcome is usually healing and necrosis and surgical debridement are rarely needed. The harm caused by oxaliplatin extravasation is not comparable to that of anthracyclines and vinca alkaloids^[10].

PREVENTION

Medical team continuing education and training

Education and training are basic elements for licensing health care professionals and for good clinical practice. They are essential to improve management and patient outcome. Education and training among nurses and physicians remains the mainstay of safe chemotherapy administration and emphasizes the importance of being *preemptive* instead of reactive to extravasation^[1,27]. In fact, the Joint Commission International emphasizes the standards of proper chemotherapy administration^[39]. Knowledge of literature and international guidelines is essential. Local institution policies should be available and stress proper administration of IV chemotherapy and prevention of accidental extravasation^[19,37]. Education of the medical team about extravasation prevention includes ensuring knowledge of risk factors, signs and symptoms, guidelines for prevention and management. Compliance to manufacturer's recommendations for each drug should be ensured by both, nurses and physicians, as well as clinical pharmacists.

Appropriate vascular access

Consideration of the appropriate vascular access is crucial for the prevention of chemotherapy extravasation. Chemotherapy infusion can be either through a central venous access or through an adequate peripheral vein. Central venous access can be accomplished through a CVAD that is placed either as an implanted port or as a peripherally inserted central catheter^[1]. CVADs are also known as Port-a-cath^[40] or polysite^[41] catheters. Veins that are small and/or fragile should be avoided as they might not withstand the required flow and rate of infusion and may have a lower threshold for extravasation. Locations that are also generally avoided include the dorsum of the hand, the antecubital fossa,

and the radial and ulnar aspects of forearm^[2,20]. Patients who do not have adequate peripheral venous access should have a central venous catheter placed^[16].

Peripheral arm assessment consists of: (1) assessing location and fragility of the patient's veins that can be reflected by the inspection and palpation of the vein. Veins that have a small caliber and/or are superficial are generally considered fragile and should be avoided. In addition, assessment also consists of (2) patient's age; (3) presence of diabetes; (4) steroid use; (5) history of previous venipunctures; (6) presence or absence of ecchymosis; (7) prior hospitalization or blood drawing history of axillary lymph nodes dissection; (8) lymphedema; (9) vascular accident in an extremity, which is the accidental puncturing of a vein. In parallel to peripheral arm assessment, the level of consciousness of the patient should be also assessed for the purpose of assuring immobility and compliance during catheter insertion^[1,2,16].

Appropriate cannula and needle selection

Selection of the appropriate cannula type and size play an important role in chemotherapy extravasation prevention. The ideal cannula is one that can remain patent to allow blood flow and that does not dislodge from its place. The recommended choice is to use the smallest size of adequate and appropriate cannula in the largest vein available. Use of 1.2-1.5 cm long small bore plastic cannula and a clear dressing that shows any possible extravasation beneath it are recommended^[42]. A butterfly needle should never be used for vesicant chemotherapy administration^[16,43].

Patient education

Since patients are the first to feel any symptoms of possible extravasation and are relied upon to report them, their education is a crucial step in chemotherapy extravasation prevention. Risk of chemotherapy extravasation should be clearly explained to patients. Physician and nurses should emphasize to the patient the importance of providing accurate history regarding previous manipulation in extremities, cooperation with the person performing the venipuncture, and reporting any symptoms that may arise during the infusion^[1,27]. Patients should be instructed to report any discomfort, pain, redness or swelling at infusion sites. Nurses and physicians should never underestimate the significance of any patient symptom and check the infusion site and venous patency immediately. Patients should also be aware of the class of drug and options of venous access and understand the higher risk of extravasation associated with it should be explained if they choose peripheral venous access over central^[1].

Guidelines for chemotherapy administration and extravasation prevention

Although there are no prospective randomized clinical trials to establish treatment of chemotherapy extravasation, management of chemotherapy extravasation

Table 3 Overall summary of guidelines for prevention of chemotherapy extravasation

Continuous education of the medical team about all policies and protocols regarding chemotherapy administration
Classification of chemotherapeutic drugs: Knowledge of characteristics of the drug and compliance to the manufacturer's recommendations
Appropriate vascular access
In case a central vascular access is not possible, an adequate peripheral vein is used ^[16]
Veins that are small and/or fragile should be avoided ^[2,20]
It is not recommended to use veins located at the dorsum of the hand, the antecubital fossa, and the radial and ulnar aspects of forearm ^[2,20]
Appropriate peripheral arm assessment ^[1,2,16]
Palpation of the vein
History of previous venipunctures
Available extremities where veins can be punctured
Level of consciousness of the patient
Appropriate equipment selection ^[42,43]
Use of the smallest size of cannula in the largest available vein
Use of 1.2-1.5 cm long small bore plastic cannula
Use of a clear dressing
Avoiding the use of a butterfly needle
Educating the patient about all risks associated with chemotherapy administration
Devising and updating standards and policies regarding chemotherapy administration at each healthcare center
Documentation and reporting of any extravasation incident

have been learnt through case reports, animal models and international clinical studies. We present relevant important statements from North American and European Guidelines published by the European Oncology Nursing Society (EONS), Oncology Nursing Society (ONS), American Society of Clinical Oncology (ASCO) and European Society of medical Oncology (ESMO)^[16,44]. In addition to International published guidelines, local institutions should have their own adapted guidelines and pathways for chemotherapy administration and also management of accidental extravasation.

ASCO and ONS: The ASCO and the ONS published safety standards for chemotherapy administration in outpatient^[19,44] and inpatient settings^[45,46]. These standards outlined the important steps in chemotherapy administration, including defining the "extravasation management procedures"^[44] prior to administration. ONS published extravasation prevention and management guidelines in the book "Chemotherapy and Biotherapy Guidelines and Recommendations for Practice", Polovich *et al.*^[11] (2009). Examples of guidelines provided are close monitoring of the infusion site every 5 to 10 min and avoiding infusion of vesicants for more than 30 to 60 min^[1]. In addition, ONS has an online course, ONS/ONCC Chemotherapy Biotherapy Certificate Course^[47] that reinforces important information to safe administration of chemotherapy and provides links to online courses, such as "Access Device: The virtual clinic", which helps better train nurses and physicians^[47]. The ASCO has a special emphasis on chemotherapy administration. It launched in 2010 the Quality Oncology Practice Initiative (QOPI) Certification Program (QCP). In the QCP report published in the Journal of Oncology Practice in March 2013, Gilmore *et al.*^[48] measured implementation of chemotherapy administration safety standards in the setting of outpatient cancer patients. Extravasation management procedures were met by 40.47% of practices. The report emphasized the

importance of availability of up-to-date extravasation management standards at the sites^[48].

ESMO and EONS: The EONS published in 2007 guidelines that can help nurses better understand extravasation^[49,50]. It conducted its sixth Spring Convention in 2008 in Geneva, Switzerland, where it launched the new guidelines for chemotherapy extravasation prevention and management. Guidelines included nurse education, assessment of venous access, assessment of equipment used, and the importance of patient education^[42,50]. This was followed by publishing guidelines developed jointly with the ESMO in 2012^[16]. Details of guidelines published are included in the following section "Management".

Local institution guidelines: These should be encouraged and include definition and diagnosis of extravasation, risk factors, guidelines for prevention, and management^[27]. For example, Cleveland Clinic has standards of chemotherapy administration clearly stated in its "Chemotherapy/Biotherapy Safe Handling Guidelines (Policy NPM-127)", which was initially published in 1996 and revised in 2007^[51]. Any local incidence of extravasation should be reported. While documentation may differ among institutions, certain items remain essential and should be documented for every incident. In addition to date and time and patient's name, name of the drug, characteristics of the solution infused, the IV access used, description of the extravasation area, signs and symptoms and management should always be documented^[16].

Table 3 summarizes guidelines for chemotherapy extravasation prevention.

MANAGEMENT

Continuous monitoring at the beginning and during the infusion is essential every 5 to 10 min. Cancer centers should ensure the availability of "Extravasation

Kits" at the treatment units. These kits should contain disposable syringes and cannulas, cold-hot packs, gauze pads, adhesive plaster, gloves, and antidotes that can be used in cases of extravasation and that will be discussed below^[3]. Management according to EONS and ONS, and few available clinical studies, are outlined below.

Initial non-pharmacologic management

In case of chemotherapy extravasation and as soon as the patient complains of pain or swelling, the first step should be immediate cessation of the infusion while keeping the cannula or port needle in place. This is followed by attempts at aspiration of the chemotherapeutic agent and removing the cannula or port needle^[3]. Aspiration of the drug is usually done by a 10 mL syringe, percutaneous needle aspiration, liposuction, simple squeeze maneuver, or by surgical fenestration and irrigation^[3,21]. Catheter can then be removed if there are no antidotes that need to be infused at the extravasated site. Elevation of the affected limb and thermal application by either cold or hot packs should follow^[28]. Elevation of the limb helps in reabsorption of the extravasated agent by decreasing capillary hydrostatic pressure and it is recommended to do during the first 24 to 48 h of the incident^[21]. It is also recommended that thermal application is performed approximately four times daily for 20 min each for 1-2 d^[42]. In addition, saline dispersion can help in diluting the vesicant by infiltrating normal saline *via* a large catheter^[21]. Taking a photo of the extravasation area helps for follow up of progress or healing process. Cold compresses can be used to reduce pain and local inflammation by causing vasoconstriction and reducing drug further spread. Cold compresses should not be used in the cases of extravasation of vinca alkaloids because it may cause further tissue damage^[14]; warm compresses and heat can be applied in incidents of vinca alkaloids extravasation as they may cause vasodilatation and absorption of extravasated drug from tissue sites.

Pharmacologic management

Dexrazoxane hydrochloride for anthracycline extravasation: Dexrazoxane is a member of the bisdioxopiperazine family and is an FDA-approved antidote for intravenous anthracycline extravasation^[52]. The exact mechanism by which it reduces tissue damage resulting from chemotherapy extravasation is unknown. There is general belief that it works through two main mechanisms. Being an analog of the iron chelator ethylenediaminetetraacetic acid that can strongly bind Iron and displace it from anthracycline, it is thought that dexrazoxane helps to reduce the oxidative stress caused by complexes of metal ions and anthracyclines^[4,53]. Also, it can exert a catalytic inhibition of topoisomerase II, the main target of anthracyclines^[53]. Dexrazoxane has been initially used to reduce the incidence of cardiomyopathy associated with anthracyclines and is approved in patients with

breast cancer responding to doxorubicin and requiring continued therapy after they exceed 300 mg/m²^[52]. Dexrazoxane is administered as a 1-2 h intravenous infusion (IV) for 3 consecutive days through a large caliber vein in a limb other than the affected one^[3,4,21] as follows: It is usually given at a dosage of 1000 mg/m² within 5 h of extravasation and then at a dosage of 1000 mg/m² on second day and 500 mg/m² on the third day following extravasation^[3,43]. To date, in addition to several case reports^[4,52], there are two large prospective multicenter clinical trials about the use of dexrazoxane in anthracyclines vesicant extravasation^[21,22,30,52]. The overall efficacy of dexrazoxane was 98%^[53]. Langer *et al.*^[41] also reported prevention of complications of doxorubicin and epirubicin extravasation by dexrazoxane. In a case of port-a-cath chest wall massive extravasation, El-Saghir *et al.*^[4] reported the successful use of dexrazoxane, for immediate relief of pain and slowing down of necrosis, along with local infiltration of granulocyte-macrophage colony-stimulating factor at the borders of the ulceration site to promote the acceleration of wound healing and reduce the need for skin grafting^[4]. The two prospective open-label single-arm studies in patients with anthracyclines extravasation were published in 2007 by Mouridsen *et al.*^[30]. Dexrazoxane was given within 6 h and repeated at 24 and 48 h. Efficacy was noted in 53 of 54 patients (98.2%) and only one patient required surgical debridement. Toxicity was manageable and includes transient elevation of liver enzymes and neutropenia that may be also due to chemotherapy itself. The use of dexrazoxane as an antidote to anthracyclines extravasation is now recommended by NCCN, EONS, ONS, and ASCO and has been formulated in a new preparation and has level III-B evidence (Evidence Level III: Evidence obtained from well-designed controlled trials without randomization; "B": Moderate strength of recommendation)^[16,54]. Doxorubicin is one of the most widely used drugs and hence has the highest potential and risk for extravasation, and, therefore, dexrazoxane should be made available at all centers that administer anthracyclines chemotherapy.

Hyaluronidase: Hyaluronidase is an enzyme that degrades hyaluronic acid in tissues and promotes diffusion of the extravasated agent. The usual dose consists of multiple subcutaneous injections of hyaluronidase 150-100 IU given as five 0.2 mL injections^[42,55]. When used for chemotherapy extravasation, it is recommended for vinca-alkaloids, etoposide^[56] and taxanes extravasation mainly^[16,23] and has level V-C evidence (Evidence Level V: Evidence from systematic reviews of descriptive and qualitative studies; "C": Poor strength of recommendation)^[16,54]. It is injected locally subcutaneously into the extravasation area.

Dimethyl sulfoxide: Dimethyl sulfoxide (DMSO) is an organosulfur solvent that is topically applied to improve absorption of the extravasated solvent^[21,49].

It also has free-radical scavenging properties^[3]. Its efficacy was observed in few studies. In a prospective study by Cassagnol *et al.*^[3], patients with anthracycline extravasation, DMSO 99% was administered twice daily for a period of 14 d and no ulcers were described^[3]. In another prospective study by Bertelli *et al.*^[56], out of a total of 122 assessable patients with extravasation of doxorubicin, epirubicin, mitomycin, mitoxantrone, cisplatin, carboplatin, ifosfamide or fluorouracil, only one patient suffered an ulceration. Treatment with DMSO was generally well tolerated with the only side effect being mild local burning and breath odor^[57]. The use of topical DMSO (99%) as an antidote to anthracycline extravasation and to Mitomycin C has level IV-B evidence (Evidence Level IV: Evidence from well-designed case-control and cohort; "B": moderate strength of recommendation)^[16,54]. DMSO is available as a solvent, and a dropper is usually used to instill drops over the affected skin. It is used as a topical application of DMSO 99% of four drops per 10 cm² to twice the size of the extravasation area^[3,22]. In cases of anthracyclines extravasation, the combination of DMSO and cooling are most commonly described initial therapy for minor anthracyclines extravasation, especially when dexrazoxane is not available.

Sodium thiosulfate: It is an antidote generally recommended for mechlorethamine (nitrogen mustard) extravasation. A study conducted by Doellman *et al.*^[21] showed that the use of sodium thiosulfate was associated with significantly improved healing time in 63 patients who had a variety of chemotherapy induced extravasation injuries, including doxorubicin, epirubicin, vinblastine, and mitomycin C^[21]. The use of sodium thiosulfate as an antidote to mechlorethamine extravasation has level V-C evidence (Evidence level V: Evidence from systematic reviews of descriptive and qualitative studies; "C": poor strength of recommendation)^[16,54]. It is usually subcutaneously locally injected in a 2 mL solution at a concentration of 0.17 mol/L^[16].

Acceleration of wound healing

Local injection of corticosteroids has been hypothesized to accelerate wound healing and prevent ulcer formation. While *in vitro* animal experimental studies showed no prevention of ulcer formation after corticosteroid injection, it was reported to have clinical benefit on ulcer prevention when used on humans^[58-61]. Variable results have been reported regarding the success of wound healing after the use of local corticosteroids, which depends on the amount of inflammatory cells generated at the site of extravasation^[62]. Local injection of granulocyte macrophage colony-stimulating factor, which is a glycoprotein growth factor, has been reported to be beneficial to wound healing in cases of doxorubicin extravasation^[4,62]. The mechanism is believed to be through stimulation of cellular components such as fibroblasts and endothelial cells^[62]. Also, local injection

of normal saline has been also mentioned as beneficial in prevention of wound ulceration after extravasation^[62].

Surgery and skin grafting

Indications for surgery in chemotherapy extravasation include full-thickness skin necrosis, chronic ulcer, and persistent pain. It is crucial that all necrotic tissue be removed until bleeding occurs and only healthy tissue left for wound coverage. To ensure complete excision, some surgeons use intraoperative fluorescent dye injection to detect the doxorubicin HCl in the tissue to ensure complete excision. After this, either immediate or delayed surgical reconstruction and skin grafting can be performed^[63].

Extravasation in the presence of CVADs

Accidental cases of extravasation in the presence of CVADs is very rare and reported in 0.24% of cases^[16]. Extravasation may occur in the subcutaneous tissue of the chest wall or neck, or in the mediastinum. Physicians and nurses should make sure that infusion needles are properly inserted in the port or chamber. In cases of extravasation in the subcutaneous tissue, infusion should be stopped immediately when patient complains of pain or swelling. Pharmacological management, including the use of dexrazoxane for anthracyclines extravasation should be instituted as reviewed in the above sections^[16]. A recent report indicated benefit from immediate removal of the CVAD along with Subcutaneous Wash-Out Procedure if extravasation is detected early, to help minimize the exposure of tissue to extravasated agent and the risk of tissue necrosis^[64]. In cases of mediastinal extravasation, ESMO guidelines include stopping the infusion, use of dexrazoxane for cases of anthracyclines, and possible surgical draining procedures for the remaining solution, antibiotics, steroids and analgesics to control symptoms from mediastinitis or pleuritic^[64].

Experimental non-pharmacologic methods

Negative pressure wound healing: Also called vacuum-assisted closure (VAC) dressing, this method applies a negative pressure to the wound, aids in aspiration of extravasated vesicant, and improves its environment. There are only few reports in which negative pressure wound healing (NPWH) was used for vesicant extravasation. Lucchina *et al.*^[65] reported a case where surgical VAC dressing was used for vinorelbine extravasation, in addition to hyaluronidase and DMSO, resulted in complete healing of the wound. In an experimental animal study conducted by Evren *et al.*^[66] on rabbits with doxorubicin extravasation, there was smaller extravasation areas in rabbits subjected to NPWH, but no histological difference compared to control rabbits.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBO) is defined by the Undersea and Hyperbaric Medical Society as a therapy consisting of intermittent breathing 100% oxygen in a

Table 4 Non-pharmacological management of chemotherapy extravasation

Institutions should always ensure availability of “extravasation kits” at floors in which chemotherapy can be given
Initial non-pharmacologic management
Continuous monitoring at the beginning and during the infusion is essential every 5 to 10 min
Aspiration of the vesicant by a 10 mL syringe, percutaneous needle aspiration, liposuction, simple squeeze maneuver, or by surgical fenestration and irrigation
Elevation of the affected limb and thermal application (cold or hot)

Table 5 Pharmacological management of chemotherapy extravasation

Dexrazoxane as an antidote to anthracyclines extravasation has level III-B evidence ^[16]
Hyaluronidase as an antidote to vinca-alkaloids and to taxanes extravasation has level V-C evidence ^[16]
Topical DMSO (99%) as an antidote to anthracycline extravasation and to Mytomicin C has level IV-B evidence ^[16]
Sodium thiosulfate as an antidote to mechlorethamine extravasation has level V-C evidence ^[16]

DMSO: Dimethyl sulfoxide.

chamber whose pressure is greater than atmospheric pressure^[67]. Its role in chemotherapy extravasation is still unclear, but it is believed that HBO increases production of oxygen free radicals and thus can aid in extravasation wound healing. In an experimental animal study conducted by Aktas *et al.*^[67] on Wistar-Albino rats for adriamycin extravasation, there was complete wound healing for 16 animals out of the 36 animals in the HBO group but no complete wound healing in any of the control group^[68].

Use of biologically synthesized nanoparticles

Recent advances in the development of chemotherapeutic agents that incorporates biologically synthesized nanoparticles have been associated with less toxicity to surrounding tissue^[31]. Nanodrugs are based on the combination of chemotherapeutic molecules with nanoparticles carriers, which include liposome, polymer, and micelle^[69]. Chemotherapeutic molecules which have been used so far for synthesis of nanoparticles include cisplatin, carboplatin, doxorubicin, 5-fluorouracil, paclitaxel, vinblastin and etoposide^[69]. For example, the use of liposomal forms of chemotherapeutic agents such as doxorubicin was associated with decreased diffusion capacity of the drug and hence less toxicity to surrounding tissue^[31,69].

Tables 4 and 5 summarize non-pharmacological and pharmacological management of chemotherapy extravasation, respectively.

CONCLUSION

Safe administration of chemotherapy and prevention of extravasation is a shared responsibility among medical team members. Education of patients about risks and manifestations are essential. Prevention of chemotherapy extravasation is an important quality indicator for certification of chemotherapy infusion centers (QOPI, ASCO). International guidelines have been published by ASCO and ONS in the United States and ESMO and EONS in Europe. While only some healthcare institutions

devise their own policies and guidelines regarding extravasation prevention and management, there is a need to have local institution education, training and guidelines. All institutions that administer intravenous chemotherapy should have known antidotes available. In spite of all efforts to prevent, accidental extravasation still occurs and more research for antidote for many drugs is needed.

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