Extravasation injury from chemotherapy and other non-antineoplastic vesicants

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INTRODUCTION

— Extravasation refers to the escape of a drug into the extravascular space, either by leakage from a vessel or by direct infiltration [1]. Although many drugs are irritating when they are introduced into extravascular tissues, extravasation of a vesicant drug has the potential to cause tissue damage with severe and/or lasting injury. Although the most well-known vesicants are cytotoxic chemotherapy drugs (table 1), several non-antineoplastic drugs also have vesicant properties (table 2).

The incidence, risk factors, clinical presentation, prevention, and management of extravasation injury from chemotherapy and non-antineoplastic vesicants are reviewed here, with a focus on chemotherapy extravasation injury. Other cutaneous complications of chemotherapy and venous irritation (chemical phlebitis) that occurs with drug administration into an intact vein (as is seen predominantly with vinorelbine and epirubicin) are discussed elsewhere. (See "Cutaneous side effects of conventional chemotherapy agents".)

INCIDENCE AND RISK FACTORS

Incidence

— The true incidence of chemotherapy vesicant extravasation is unclear since there is no central reporting mechanism. With an increasing awareness of the risks from extravasation, the frequency appears to have fallen.

Data from MD Anderson Cancer Center indicate that the rate of serious extravasation injury (as determined by referral patterns to a plastic surgery clinic) declined from 0.1 to 0.01 percent over a 15-year period, based upon individual doses of chemotherapy administered [2]. However, this series only includes patients who were referred to plastic surgery, rather than all extravasations, while the denominator includes all individual doses of chemotherapy delivered over the six-year study period. As such, this rate probably

underestimates the true incidence of chemotherapy extravasation injury. Furthermore, this rate may not reflect the actual rate in other clinical settings.

Infusional administration of vesicant antineoplastic agents is frequently done through a central venous access device (CVAD) to minimize the likelihood of subcutaneous extravasation. While the risk of chemotherapy extravasation through a CVAD is small, it is not zero, and extravasation may be due to injection technique or device failure:

- In a single-center report of 376 patients receiving high-dose chemotherapy and peripheral blood stem cell transplantation through a CVAD over a five-year period, there was one case of extravasation (0.26 percent) [3].
- Another series noted three extravasations in 225 CVADs implanted in 217 patients over an 11-year period (1.3 percent) [4].
- A third report noted 15 cases of drug extravasation among 815 consecutive cancer patients (1.8 percent) who received chemotherapy with a totally implantable venous access port system over a one-year period, not all of whom were receiving vesicants [5].

The incidence of extravasation among individuals receiving non-neoplastic vesicant medications is unknown.

Risk factors

— Every patient who receives a vesicant is at risk for extravasation. Risk factors for extravasation from a peripheral vein include [6-8]:

- Small and/or fragile veins, or limited vein availability because of lymph node dissection, lymphedema, or limb removal.
- Obesity, which obscures veins from view and palpation.
- Multiple previous venipunctures.
- Disseminated skin disease (eg, eczema, psoriasis).
- Patient movement.
- Sensory deficits that impair a patient's ability to detect a change in sensation at the site of chemotherapy administration (eg, paralysis, prior stroke, sedation, somnolence, impaired cognition, impaired mental status).

Risk factors for extravasation from a CVAD include [7,9,10]:

- Difficulty encountered during insertion of the device, such as probing or inability to advance the guidewire or catheter. Catheters can also become inadvertently sliced, pierced, or nicked before or during insertion.

- Device misplacement, with the catheter tip placed outside of the venous system instead of the superior vena cava.
- Catheter migration from the vein into the tissue.
- Long dwell time (six months or longer); soft catheter materials are prone to weakening and "pinch off" syndrome, which occur when the catheter is compressed between the clavicle and the first or second rib.
- The presence of a fibrin sheath or thrombus at the catheter tip, which may cause vesicant chemotherapy to backtrack along the catheter and leak from the vein at the venotomy site.
- A deeply implanted port, which increases the risk that a non-coring needle will be of insufficient length to be correctly positioned into the port septum or that patient movement will cause "rocking" of the needle within the port septum.

IRRITANTS VERSUS VESICANT DRUGS

Antineoplastic agents

— Cytotoxic drugs are classified based upon their potential for local toxicity (table 1) [11,12]:

- Vesicants – Extravasation of a vesicant drug has the potential to cause tissue necrosis with a more severe and/or lasting injury. Vesicant extravasation may result in loss of the full thickness of the skin and, if severe, underlying structures. The anthracyclines are among the most important cytotoxic chemotherapy agents that cause extravasation injury, because of their widespread use in various chemotherapy regimens and their ability to produce severe tissue necrosis.
- Irritants – An irritant drug causes an inflammatory reaction, with aching, burning, tightness, pain, and phlebitis at the needle insertion site or along the vein. Clinical signs include warmth, erythema, and tenderness in the extravasated area, but without tissue sloughing or necrosis. Symptoms are usually of short duration, and there are no long-lasting sequelae. Some irritants can cause tissue necrosis if large volumes of concentrated solutions are extravasated.

The distinction between irritant and vesicant chemotherapy drugs is not absolute. As examples:

- There are reports of tissue injury from an extravasation of oxaliplatin [13,14], although another series of 11 patients showed no tissue destruction [15].
- Most injection site reactions following extravasation of paclitaxel consist of redness, tenderness, and swelling, but there are case reports that document necrosis and skin exfoliation [16-19]. Only rarely are long-term sequelae reported, such as ulceration requiring surgical intervention [20]. In a compilation of 35 reported cases of paclitaxel extravasation, only three developed ulceration, two requiring skin closure [16]. While most references classify paclitaxel as an irritant drug, the Oncology

Nursing Society (ONS) and Multinational Association of Supportive Care in cancer (MASCC) classify it as a vesicant [21,22].

- Mitoxantrone, usually classified as an irritant, has been reported to cause skin necrosis requiring surgical debridement and skin grafting [23].

- Ado-trastuzumab emtansine, an antibody-drug conjugate that consists of the anti-human epidermal growth factor receptor 2 (HER2) monoclonal antibody trastuzumab conjugated to emtansine, a highly cytotoxic antimicrotubule agent, has been classified as an irritant; however, a single case report of skin necrosis following subcutaneous extravasation has been reported [24].

In such cases, the extent of tissue injury may be a function of the amount of drug extravasated.

Non-antineoplastic agents

— Although extravasation from vesicants is best described with antineoplastic agents, a number of other non-antineoplastic drugs can also act as vesicants or irritants if they extravasate into the subcutaneous tissues (table 2) [25-28].

MANIFESTATIONS

— Early symptoms and signs of extravasation injury from a vesicant are often subtle. They usually appear immediately after the extravasation but can be delayed for days to weeks [25]. Initially, there is local burning or tingling at the infusion site, mild erythema, pruritus, and swelling. Within two to three days, increased erythema, pain, brawny discoloration, induration, dry desquamation, and/or blistering may appear [29].

With a small volume of extravasation, symptoms may disappear over several weeks. With more extensive infiltrations, necrosis, eschar formation, and ulceration with raised, red, painful edges and a yellow necrotic base may develop over several weeks.

Vesicant-induced ulcerations lack granulation tissue and have little epithelial ingrowth. While very small ulcers typically heal gradually, larger lesions tend to persist, gradually expanding over time. If left untreated, underlying tendons, nerves, and vessels may become involved, potentially leading to nerve compression syndromes, permanent joint stiffness, contractures, and neurologic dysfunction [25].

There have been reports of an extravasation recall phenomenon, where previous sites of extravasation of a vesicant drug become inflamed upon re-exposure of the patient to the same drug administered at a remote intravenous site. This phenomenon has been reported with paclitaxel [30-32], doxorubicin [33,34], epirubicin [35], and docetaxel [36,37].

The severity of extravasation can be divided into four grades, as outlined in the table (table 3).

Central venous access device extravasation

— When extravasation occurs from a central venous access device (CVAD), the extravasated solution may accumulate in the mediastinum, the pleura, or the subcutaneous tissues of the chest or neck. The predominant symptom is thoracic pain.

PREVENTION

— The best approach to extravasation injury is prevention [9]. Guidelines for prevention of chemotherapy extravasation are available from the Oncology Nursing Society (ONS) and the European Oncology Nurses Society (EONS) [11,21]. Several simple precautions can minimize the risk of extravasation:

- For peripheral infusions of chemotherapy, the intravenous (IV) line should be recently started, and the vein selected should be large and intact, with good blood return established prior to starting the infusion.
- Infusion sites should be selected in the following order of preference: forearm (basilic, cephalic, and median antebrachial), dorsum of hand, wrist, antecubital fossae. With vesicants, try to avoid the antecubital fossa, wrist, and dorsum of the hand, if at all possible. Contractions from vesicant extravasation in these regions can cause serious long-term morbidity.
- Sites with sclerosis, thrombosis, or scar formation should be avoided, as should limbs with impaired circulation. Although controversial, most experts do not feel that the avoidance of IV lines on the ipsilateral side is necessary or beneficial in a woman who has undergone mastectomy for breast cancer as long as lymphedema is absent. (See "Clinical staging and conservative management of peripheral lymphedema".)
- The butterfly needle or plastic cannula should be secured to the skin with tape. Taping of the entry site itself should be avoided so that the area can be examined. Instead, once the hub of the cannula or butterfly needle is secured to the skin with tape, a clear dressing, such as Tegaderm, should be applied to cover the skin entry site.
- The patency of the IV line should be verified just prior to drug infusion by flushing with 5 to 10 mL of isotonic saline or a 5 percent dextrose solution.
- Instruct the patient to notify a clinician immediately if he or she experiences any pain, leaking, or other changes in sensation at the infusion site. Ensure that there are no barriers to effective communication. For patients with central venous catheters, this may include chest pain or dyspnea from pleural effusion if the tip should penetrate the superior vena cava.
- The chemotherapeutic agent, appropriately diluted, should be infused through the side arm of the freely-flowing IV with isotonic saline or 5 percent dextrose. During the infusion, patients should be closely monitored for pain (often described as mild to severe burning radiating along the vein), and the site should be inspected for erythema or swelling [6].

- Use of a central venous catheter for infusion of vesicant drugs provides reliable venous access, high flow rates, and rapid drug dilution. However, these vascular access devices are subject to a number of complications, including drug extravasation. The catheter tip may not be properly positioned in the superior vena cava or right atrium, it may migrate out of position, the needle may be improperly inserted into the injection port, or the catheter itself may be punctured or may rupture [38]. The position of a catheter following surgical placement should be confirmed radiographically prior to drug administration. In addition, if there are any complaints of pain, even without soft tissue swelling or the lack of ability to draw blood or infuse a flush solution, there is a need to reconfirm the positioning of the catheter prior to continuing with the chemotherapy infusion.

- Previously irradiated areas should be avoided whenever possible.

MANAGEMENT

— There are no randomized trials that have established the role of specific interventions in the management of chemotherapy extravasation [39,40]. Information regarding the treatment of chemotherapy extravasation is based upon animal models, anecdotal case reports, and a limited number of small uncontrolled studies [40]. Furthermore, evaluation of the published data in humans is difficult due to variability in methods and treatment endpoints, and the confounding influence of nonpharmacologic therapy (ie, the application of cold or heat).

Guidelines for management of chemotherapy extravasation are available from the Oncology Nursing Society (ONS) and the European Oncology Nurses Society (EONS) [11,21]. The ONS standards were initially developed in 2009 [41] and were reiterated in 2011 and 2013 with little, if any, change [42,43]. The use of a standardized protocol will allow most extravasations to be managed conservatively, minimizing the need for surgical intervention [44].

An overview of our recommended approach to the management of chemotherapy extravasations, which follows the general guidelines of the ONS and EONS, is presented in the table (table 4).

Initial management

— When extravasation of an irritant or vesicant drug is suspected, the following initial management is recommended [11,21,45,46]:

- Stop the infusion immediately. Do not flush the line, and avoid applying pressure to the extravasated site.

- Elevate the affected extremity.

- The catheter/needle should **not** be removed immediately. Instead, it should be left in place to attempt to aspirate fluid from the extravasated area and to facilitate the administration of an antidote to the local area, if appropriate (see below).

- If an antidote will not be injected into the extravasation site, the catheter/needle can be removed after attempted aspiration of the subcutaneous tissues.

Application of heat or cold

— Topical application of ice or cold packs is recommended for extravasation of all vesicant or irritant drugs **except** the vinca alkaloids (vincristine, vinblastine, vinorelbine) and epipodophyllotoxins such as etoposide. Intermittent cooling is thought to cause vasoconstriction, thereby diminishing the spread of the drug and the extent of the local injury [47]. Cold compresses also reduce local inflammation and pain.

Efficacy of cold application was suggested in a series of 175 patients with extravasation of a variety of chemotherapeutic agents, in which close to 90 percent of those treated with ice alone (15 minutes four times daily for three days) required no further therapy [48].

Application of ice is **contraindicated** for extravasations of vinca alkaloids or epipodophyllotoxins, as cold worsens the ulceration caused by these drugs, at least in animal models [47,49]. Instead, the application of heat is generally recommended for these agents, although most of the available data are derived from animal studies rather than clinical reports. Local heating is thought to result in localized vasodilation and increased blood flow, thereby enhancing drug removal [49].

The role of heat versus cold with taxanes is less clear:

- For paclitaxel extravasations, some guidelines suggest the application of ice [16,21], although EONS/European Society for Medical Oncology (ESMO) guidelines suggest application of heat in this setting, since the taxanes, like the vinca alkaloids, are non-DNA binding agents and the general strategy for these types of extravasations is to dilute and diffuse [11]. Aside from extravasation recall phenomena, long-term effects of paclitaxel extravasation are minimal and usually entail mild fibrosis around the extravasation site.

- Skin toxicity, including desquamation following accidental extravasation, is more frequent with docetaxel than paclitaxel, although serious long-term sequelae have not been described. The relative benefit of topical cooling for docetaxel extravasations is less clear than for paclitaxel; some (including the EONS) suggest that heat rather than cold be applied in such cases [11,50].

Specific antidotes

— Specific antidotes have been recommended to prevent necrosis and ulceration following extravasation of certain drugs, although none of these have been validated in randomized clinical trials (table 4). These include:

- Systemic administration of dexrazoxane following anthracycline extravasation

- Topical application of dimethylsulfoxide (DMSO) for anthracycline extravasation when dexrazoxane is not immediately available

- Local injection of sodium thiosulfate for extravasations of mechlorethamine, dacarbazine, and cisplatin
- A single, subcutaneous, local injection of DMSO for mitomycin extravasation, followed by topical application [6]
- Local injection of hyaluronidase for extravasations of vinca alkaloids, paclitaxel, epipodophyllotoxins, and ifosfamide

For other drugs (eg, trabectedin [51]), there are no specific published antidotes [52].

Dexrazoxane

— Dexrazoxane has been approved by both the European Agency for the Evaluation of Medicinal Products and the US Food and Drug Administration (FDA) for the treatment of anthracycline extravasation injury. Treatment should be started as soon as possible and within the first six hours after extravasation.

Benefit for dexrazoxane after anthracycline extravasation was initially suggested in animal studies and isolated case reports [53-56]. Dexrazoxane was subsequently evaluated in two prospective, nonrandomized, multicenter studies involving 80 patients with presumed anthracycline extravasations [57]. Dexrazoxane was administered intravenously as three one- to two-hour infusions through a different venous access location, with the first dose given within six hours of the actual extravasation, and subsequent doses administered 24 and 48 hours after extravasation. The first and second doses were 1000 mg/m^2, and the third dose was 500 mg/m^2, up to maximum total doses of 2000, 2000, and 1000 mg, respectively.

Extravasation was confirmed by fluorescence microscopy of a biopsy specimen in 54 cases. Only one patient (2 percent) who received therapy within six hours after the event required surgical debridement. The most frequent sequelae of the extravasations were mild pain and sensory disturbances (19 and 17 percent, respectively). Chemotherapy was able to be continued without interruption in 71 percent of cases.

Extravasation of liposomal anthracycline preparations (daunorubicin or doxorubicin) is generally not associated with necrotic injury [58,59]. Application of ice alone to reduce local inflammation (and avoidance of DMSO) is recommended (table 4). However, for the rare patient who develops symptomatic extravasation of pegylated liposomal doxorubicin, dexrazoxane may be beneficial [60].

Sodium thiosulfate

— Local injection of a freshly prepared 4 percent (1/6 Molar) or 2 percent solution of sodium thiosulfate (2 mL for each mg thought to be extravasated) is recommended for the treatment of mechlorethamine (nitrogen mustard) extravasations, as well as for large-volume extravasation of concentrated dacarbazine or cisplatin (table 4) [21,46,61]. The solution is injected subcutaneously into the extravasated site using a separate 25 gauge or smaller needle.

To make a 4 percent solution:

- If using 10 percent sodium thiosulfate, mix 4 mL with 6 mL sterile water for injection.
- If using 25 percent sodium thiosulfate, mix 1.6 mL with 8.4 mL sterile water for injection.

The recommendation for use of thiosulfate is based largely on in vitro data demonstrating an interaction of thiosulfate with both cisplatin and mechlorethamine, and in vivo animal data demonstrating the ability of thiosulfate to inactivate mechlorethamine [62-66].

The clinical benefit of thiosulfate in patients with mechlorethamine extravasation is poorly documented, with one report demonstrating protection from ulceration in a single patient who received an inadvertent intramuscular injection [67]. Nevertheless, both the ONS and EONS recommend the use of sodium thiosulfate for mechlorethamine extravasation despite the lack of conclusive evidence as to benefit [11,21].

In addition, use of sodium thiosulfate has also been suggested for extravasations of bendamustine (a mechlorethamine derivative that usually acts as an irritant but can cause local tissue injury if extravasated) [7]. However, neither the ONS nor EONS has addressed the issue of sodium thiosulfate with this drug [11,21].

Clinical efficacy of sodium thiosulfate in patients with extravasation from other agents was suggested in a series of 63 patients who had received doxorubicin, epirubicin, vinblastine, or mitomycin C [61]. One-half were treated with hydrocortisone and dexamethasone (see below) alone, while the remainder also received sodium thiosulfate (2 percent solution injected subcutaneously). No patient in either group developed skin ulceration or required surgery. The mean healing time for the group receiving thiosulfate was one-half that of the other group, although the lack of randomization in treatment assignment renders this result inconclusive.

Hyaluronidase

— For extravasations of vinca alkaloids, paclitaxel, and docetaxel, we suggest local injection of hyaluronidase.

The proteolytic enzyme hyaluronidase promotes the diffusion of subcutaneously injected solutions by hydrolyzing hyaluronic acid, one of the chief ingredients of the connective tissue stroma. It is postulated that this creates a wider surface for dilution and aspiration of the drug.

The evidence supporting the use of local infiltration with hyaluronidase for extravasations with these chemotherapy agents is based upon small series and case reports [11,16,68]. In one published study of six patients with extravasation of a vinca alkaloid (vinorelbine, vinblastine, vincristine), pain resolved within several days of the extravasation in all six without the application of cold compresses [68]. A review of reports of treatment of paclitaxel extravasation found inconsistent results with hyaluronidase [16]. In a series of four cases, two managed with cold compresses with hyaluronidase injections around the extravasated area and two treated with cold compresses alone, the use of hyaluronidase was associated with delayed healing. In contrast, in another small series, there was a complete disappearance of local

symptoms (pain, erythema, swelling) with the use of hyaluronidase for a paclitaxel extravasation in five patients.

While EONS suggests the use of hyaluronidase for extravasations of taxanes and vinca alkaloids [11], guidelines for treatment of extravasation from the ONS recommend hyaluronidase only for extravasations of vinca alkaloids, and not other agents [21].

Single case reports also support potential benefit with extravasations from phenytoin [69], nafcillin [70], and other compounds, such as mannitol and high concentrations of dextrose [68,71-74].

Preparations of hyaluronidase are commercially available but have not been approved for this indication. The recommended dose is 1 mL (150 units), infiltrated subcutaneously, as five separate injections of 0.2 mL each, into the extravasated site along the leading edge of the erythema, using a separate 25 gauge or smaller needle.

DMSO

— Guidelines for extravasation management from the ONS do not include DMSO [21], and even the manufacturers' package labeling information fails to recommend its use for anthracycline or mitomycin extravasations. DMSO was also not included in the recommended treatments for extravasation in 2012 guidelines from ESMO/EONS [11]. However, a subsequent letter to the editor by the author of these guidelines seemed to reverse this position, stating that although the studies with dexrazoxane reflected a slightly superior level of evidence than those with DMSO, both treatments could be considered for the treatment of an anthracycline extravasation through a peripheral line [75].

In our view, DMSO (where available) represents an acceptable treatment for mitomycin extravasation, and an alternative to dexrazoxane for peripheral anthracycline extravasations if dexrazoxane is unavailable or if dexrazoxane cannot be started within six hours of the actual extravasation event (table 4). There is no evidence that combined use of dexrazoxane and topical DMSO is of any benefit in patients with anthracycline extravasations. (See 'Dexrazoxane' above.)

The evidence supporting the use of DMSO comes from two observational studies in patients with chemotherapy extravasations, both of which used topical administration:

- In the largest series, 144 patients with chemotherapy extravasation from a variety of drugs received topical DMSO (application of a 99 percent solution every eight hours for seven days) plus local cooling therapy (60 minutes every eight hours for three days) [76]. The authors reported complete recovery within one week in 103 patients (71 percent), while 22 others recovered with more prolonged DMSO therapy (total success rate 87 percent). Ulceration developed in a sole patient with an epirubicin extravasation. Interpretation of these results is difficult because of the combined use of both DMSO and topical cooling. Furthermore, only 62 extravasations were due to known vesicants (doxorubicin, mitomycin, or epirubicin), while the remainder involved irritant rather than vesicant drugs (cisplatin, ifosfamide, mitoxantrone).

- Benefit for DMSO independent of cold application in patients with anthracycline extravasation was also suggested in a prospective series in which 0 of 20 patients who received topical DMSO (99 percent solution every six hours for 14 days) developed ulceration or required surgical management [77].

The mechanism underlying benefit from DMSO is uncertain. DMSO has activity as a free radical scavenger, and at least some data support the view that tissue damage from vesicants (particularly anthracyclines) is due to the formation of hydroxyl free radicals [78,79]. The two studies cited above both used a DMSO concentration of >90 percent, which is not available in the United States. The only available preparation is a 50 percent solution, which is marketed for intravesical use.

Corticosteroids

— In general, corticosteroids are not indicated in the management of vesicant extravasations, with the possible exception of large-volume extravasations of oxaliplatin. This position is consistent with recommendations from the ONS and EONS [11,21].

For patients with anthracycline extravasation, systemic, subcutaneous, and intradermal administration of corticosteroids at the extravasation site have been advocated in the past, although whether there is benefit for this approach is unclear. Interpretation of the published literature is confounded by variability in dose and duration of therapy, route of administration, and outcome measurement [25]. Corticosteroids are presumed to reduce local inflammation, but it has never been shown that tissue damage from vesicant extravasation is the result of an inflammatory process.

The lack of consensus on the benefit of corticosteroids for anthracycline extravasation is illustrated by the fact that product labeling information from two of three suppliers of doxorubicin, as well as daunorubicin and idarubicin, do not recommend corticosteroids as a component of extravasation management.

One circumstance where oral corticosteroids may be of benefit is in patients who have extravasated large amounts of oxaliplatin. In one series of five such patients, the early administration of high-dose oral dexamethasone (8 mg twice daily for up to 14 days) appeared to have a beneficial effect on the severity and clinical course of the inflammatory reaction [15].

Corticosteroids may worsen the skin damage from etoposide or vinca alkaloids, and they are specifically contraindicated in these situations.

Surgical intervention

— Nonhealing ulcers resulting from an extravasation injury often require debridement and skin grafting. However, the optimal timing of surgical intervention is controversial.

There are no uniform guidelines for the surgical treatment of extravasation injuries. Guidelines from the ONS do not address indications for surgical management [21]. Guidelines from the EONS recommend surgical debridement for unresolved tissue necrosis or pain lasting more than 10 days [11], but whether

surgical intervention is recommended in a patient complaining of persistent pain in the presence of normal-looking skin is unclear.

Although some clinicians suggest early surgical intervention to prevent ulceration [29,80], a conservative approach is more often recommended [45,81-85], particularly since fewer than one-third of vesicant extravasations ultimately result in ulceration. Failure of initial conservative management with continued erythema, swelling and pain, or the presence of large areas of tissue necrosis or skin ulceration are indications for surgery [81,86].

Issues unique to central venous access device extravasation

— There are only case report data regarding the evolution and management of extravasation through a central venous access device (CVAD). The diagnosis may be confirmed by imaging, typically with a thoracic computed tomography (CT).

Management should include stopping the infusion and aspirating through the CVAD catheter as much of the solution as possible. If the extravasated agent is an anthracycline, intravenous dexrazoxane could be considered as an antidote. The utility of local antidotes (hyaluronidase, sodium thiosulfate) is unclear, and their use is not recommended in guidelines from the EONS [11].

A CT scan should be obtained; catheter tip migration through the superior vena cava or atrium is a surgical emergency and requires immediate operation. If there is no evidence of suppurative mediastinitis, one would assume that the process is sterile, and therefore, conservative management is reasonable. Indications for operative intervention include failure of response to conservative/supportive treatment, as indicated by the development of sepsis, progression of the radiographic abnormalities concurrent with clinical deterioration, and clinical deterioration in the setting of a collection or necrotic area, even if it appears "improved" on radiographic imaging.

The only data on surgical intervention for extravasation from CVAD come from published case reports [18,38,87-91]. Options include debridement of all necrotic material with the establishment of drainage and antibiotic therapy, and if extravasation is detected early, immediate removal of the port along with an intraoperative subcutaneous washout to help minimize the exposure of tissue to the extravasated agent and the risk of tissue necrosis [91]. In our view, decisions about whether to pursue an early subcutaneous washout procedure must be individualized, carefully weighing the need to retain the port for central venous access versus the risk of skin adverse events.

EONS guidelines recommend immediate surgical consultation with consideration of thoracentesis and/or chest tube placement if the extravasation is into the pleura, thoracoscopy or thoracotomy for an extravasation into the mediastinum, and surgical drainage of the accumulated solution in the case of a subcutaneous fluid collection [11]. However, cases of mediastinal extravasation of anthracyclines have resolved with conservative therapy [90,92].

SUMMARY AND RECOMMENDATIONS

- Proper infusion technique is the most important component of preventing extravasation injury from chemotherapy and other non-neoplastic vesicants. (See 'Prevention' above.)

- If extravasation of a vesicant agent is suspected, initial management should focus on minimizing the extent of drug extravasation (see 'Initial management' above):

  - Stop the infusion immediately. Do not flush the line, and avoid applying pressure to the extravasated site.

  - Elevate the affected extremity.

  - The catheter/needle should **not** be removed immediately. Instead, it should be left in place to attempt to aspirate fluid from the extravasated area and to facilitate the administration of an antidote to the local area, if appropriate (see below).

  - If an antidote will not be injected into the extravasation site, the catheter/needle can be removed after attempted aspiration of the subcutaneous tissues.

- For extravasations of vesicant agents other than the vinca alkaloids and etoposide, we suggest the topical application of cold (**Grade 2C**) (table 4). For the vinca alkaloids and etoposide, we suggest the application of heat rather than cold (**Grade 2C**). (See 'Application of heat or cold' above.)

- For extravasation of anthracyclines that have a high likelihood of producing tissue ulceration (ie, non-liposomal preparations), we recommend systemic administration of dexrazoxane (**Grade 1B**). Liposomal anthracyclines are generally not associated with necrotic injury, and treatment with dexrazoxane is not indicated in this situation, except in the rare situation of a symptomatic extravasation. (See 'Dexrazoxane' above.)

- For extravasations of oxaliplatin, we suggest the administration of high doses of oral corticosteroids (dexamethasone 8 mg twice daily for up to 14 days) (**Grade 2C**). (See 'Corticosteroids' above.)

- For extravasation of mechlorethamine, bendamustine, dacarbazine, or cisplatin, we suggest local injection of sodium thiosulfate (**Grade 2C**). (See 'Sodium thiosulfate' above.)

- For extravasations of vinca alkaloids and taxanes (paclitaxel, docetaxel), we suggest local injection of hyaluronidase (**Grade 2C**). (See 'Hyaluronidase' above.)

- The optimal approach to local therapy for extravasation of non-neoplastic vesicants is unclear, and there are no guidelines. While the available data are limited to case reports with a few drugs (ie, nafcillin, phenytoin, mannitol, high concentrations of dextrose), local injection of hyaluronidase represents a reasonable approach.

- There are no uniform guidelines for the surgical treatment of extravasation injuries; failure of initial conservative management with continued erythema, swelling and pain, or the presence of large areas of tissue necrosis or skin ulceration are indications for surgical management. For central venous access device (CVAD) extravasations, computed tomography (CT) scanning and surgical consultation are

indicated, although no specific plan of treatment has been supported through published studies. (See 'Surgical intervention' above.)

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