Safe Management of Chemotherapy: Infusion-Related Complications

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Extravasation

1. Pathophysiology: Tissue damage secondary to vesicant infiltration or leakage outside of the vessel that occurs as a result of one of two major mechanisms
   a) The vesicant binds to nucleic acids in the DNA of healthy cells in the tissue, causing cell death. The dead cells release complexes, which are taken up by adjacent healthy cells. This process of cellular uptake of extracellular substances sets up a continuing cycle of tissue damage as the DNA-binding vesicant is retained and recirculated in the tissue for a long period of time (Luedke, Kennedy, & Rietschel, 1979). Examples of DNA-binding vesicants include anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin), actinomycin, mechloroethamine (nitrogen mustard), mitomycin, and mitoxantrone.
   b) The vesicant does not bind to cellular DNA. The vesicant has an indirect rather than direct effect on the cells in healthy tissue. It is eventually metabolized in the tissue and is more easily neutralized than DNA-binding vesicants (Ener, Meglathery, & Styler, 2004). Examples of non–DNA-binding vesicants include plant alkaloids (vinblastine, vincristine, vindesine, vinorelbine) and taxanes (docetaxel, paclitaxel, paclitaxel protein-bound particles for injectable suspension), which are mild vesicants.

2. Factors affecting tissue damage severity
   a) Type of vesicant extravasated (DNA-binding or nonbinding)
   b) Concentration and amount of vesicant in the tissue
   c) Location of extravasation
   d) Patient factors, such as older age, comorbidity (e.g., diabetes), and impaired immunocompetence (Ener et al., 2004; Schulmeister, 2011)

3. Risk factors for peripheral extravasations (Goolsby & Lombardo, 2006; Sauerland, Engelking, Wickham, & Corbi, 2006)
   a) Small, fragile veins
   b) Previous multiple venipunctures
   c) Prior treatment with irritating or sclerosing drugs, such as chemotherapy
   d) Sensory deficits
   e) Limited vein selection because of lymph node dissection, lymphedema, or limb removal
   f) Impaired cognition, altered mental status (impairs ability to detect administration site sensation changes), or somnolence
   g) Probing during IV catheter insertion
   h) Inadequately secured IV catheter
   i) Administration site in areas with minimal overlying tissue (e.g., dorsum of the hand, wrist, or antecubital area)
   j) Use of rigid IV devices (e.g., steel-winged “butterfly” needles)

4. Possible etiologies of peripheral extravasations (Sauerland et al., 2006)
   a) Vein wall puncture, piercing, or trauma
   b) Dislodgment of the catheter from the vein
   c) Administration of a vesicant in a vein below a recent (less than 24 hours) venipuncture site
   d) Administration of a vesicant in a vein below a recent or nonhealed vesicant extravasation site
   e) Inadvertent intramuscular (IM) or subcutaneous (SC) vesicant administration

5. Risk factors for extravasation from central VADs (Sauerland et al., 2006)
   a) Difficulty encountered during device insertion (e.g., probing during venipuncture, inability to advance guidewire or catheter)
   b) Inadvertent slicing, piercing, or nicking of catheter prior to or during insertion
   c) Device misplacement with catheter tip outside of the venous system
   d) Inadequately secured noncoring needles (implanted ports)
   e) Deeply implanted ports
   f) Presence of a fibrin sheath or thrombus at the catheter tip
   g) Catheter migration
   h) Long dwell time of catheters inserted using a subclavian approach
Possible etiologies of extravasations
from central VADs (Goossens, Stas, Jérôme, & Moons, 2011; Sauerland et al., 2006)

a) Vein perforation
b) Catheter leakage, rupture, or fracture
c) Separation of the catheter from a portal body (implanted ports)
d) Incomplete insertion of a noncoring needle into an implanted port
e) Noncoring needle dislodgment from an implanted port
f) Backflow of vesicant along the catheter to the venotomy site secondary to fibrin sheath or thrombus at the catheter tip

Signs and symptoms of vesicant extravasation: Irritation of the vein and flare reactions may mimic some of the signs and symptoms of vesicant extravasation (see Table 1). Irritation of the vein and flare reactions are unique to peripheral chemotherapy administration; they do not occur when chemotherapy is administered via central VADs because the chemotherapy is rapidly diluted in large veins (Wickham, Engelking, Sauerland, & Corbi, 2006). Signs and symptoms of vesicant extravasation are found in Table 1. Additional signs and symptoms include the following (Ener et al., 2004).

- **Immediate:** Pain typically occurs and is described as burning, stinging, or a sensation of coolness at and around the vesicant administration site. However, some patients do not experience pain when a vesicant extravasates. Delayed: Pain usually increases in intensity over time.
- **Immediate:** Redness in the area of the vesicant administration site commonly occurs but is not always present or may be difficult to detect if the extravasation is occurring deeper in the tissue (e.g., as a result of needle dislodgment from implanted port). Delayed: Redness generally intensifies over time.
- **Immediate:** Swelling commonly is observed and is easier to detect when extravasation is superficial (e.g., from a peripheral vein) rather than deep in the tissue (e.g., implanted ports). Delayed: Swelling typically increases over time.
- **Immediate:** Loss of blood return from IV device occurs. Blood return should be present. If loss of blood return occurs, suspect infiltration of irritant.
- **Immediate:** Ulceration does not occur. Ulceration does not occur.

**TABLE 1. Signs and Symptoms Associated With Vesicant Extravasation, Venous Irritation, and Flare Reaction**

<table>
<thead>
<tr>
<th>Signs/Symptoms</th>
<th>Vesicant Extravasation</th>
<th>Venous Irritation</th>
<th>Flare Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Pain</strong></td>
<td>Immediate: Pain typically occurs and is described as burning, stinging, or a sensation of coolness at and around the vesicant administration site. However, some patients do not experience pain when a vesicant extravasates. Delayed: Pain usually increases in intensity over time.</td>
<td>Aching and tightness along a peripheral vein, above the administration site, occurs as the drug infuses.</td>
<td>No pain; the skin overlying the vein may itch.</td>
</tr>
<tr>
<td><strong>Redness</strong></td>
<td>Immediate: Redness in the area of the vesicant administration site commonly occurs but is not always present or may be difficult to detect if the extravasation is occurring deeper in the tissue (e.g., as a result of needle dislodgment from implanted port). Delayed: Redness generally intensifies over time.</td>
<td>The vein may appear reddened or darkened.</td>
<td>Immediate blots or streaks develop along the vein, which usually subside within a few minutes. Wheals may appear along the vein.</td>
</tr>
<tr>
<td><strong>Swelling</strong></td>
<td>Immediate: Swelling commonly is observed and is easier to detect when extravasation is superficial (e.g., from a peripheral vein) rather than deep in the tissue (e.g., implanted ports). Delayed: Swelling typically increases over time.</td>
<td>Swelling does not occur.</td>
<td>Swelling does not occur.</td>
</tr>
<tr>
<td><strong>Blood return</strong></td>
<td>Immediate: Loss of blood return from IV device occurs.</td>
<td>Blood return should be present. If loss of blood return occurs, suspect infiltration of irritant.</td>
<td>Blood return is present.</td>
</tr>
<tr>
<td><strong>Ulceration</strong></td>
<td>Immediate: Skin integrity is intact. Delayed: If vesicant extravasation is not treated, blistering and sloughing begin within 1–2 weeks, followed by tissue necrosis that may require surgical debridement and skin grafting or flap placement.</td>
<td>Ulceration does not occur.</td>
<td>Ulceration does not occur.</td>
</tr>
</tbody>
</table>

**Note.** Based on information from Goolsby & Lombardo, 2006; Sauerland et al., 2006; Schulmeister, 2011.
TABLE 2. Vesicant Extravasation Management Guidelines

<table>
<thead>
<tr>
<th>Classification/Drug</th>
<th>Immediate Topical Therapy</th>
<th>Antidote or Treatment</th>
<th>Antidote or Treatment Administration, Patient Monitoring, and Follow-Up</th>
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<tr>
<td>Alkylating agent</td>
<td>Apply ice for 6–12 hours following sodium thiosulfate antidote injection (Lundbeck, 2012).</td>
<td>Antidote: Sodium thiosulfate. Mechanism of action: Neutralizes mechloretamine to form nontoxic thioesters that are excruted in the urine. Preparation: Prepare 1/6 molar solution. If 10% sodium thiosulfate solution: Mix 4 ml with 6 ml sterile water for injection. If 25% sodium thiosulfate solution: Mix 1.6 ml with 8.4 ml sterile water. Storage: Store at room temperature between 15°C–30°C (59°F–86°F).</td>
<td>Inject 2 ml of the sodium thiosulfate solution for each milligram of mechloretamine suspected to have extravasated. Inject the solution subcutaneously (SC) into the extravasation site using a 25-gauge or smaller needle (change needle with each injection). Assess the extravasation area for pain, blister formation, and skin sloughing periodically as needed or in accordance with institutional policy. Instruct the patient to monitor the extravasation site and report fever, chills, blistering, skin sloughing, and worsening pain. Instruct the patient with peripheral extravasations to report arm or hand swelling and stiffness.</td>
</tr>
<tr>
<td>Anthracenedione</td>
<td>Apply ice pack for 15–20 minutes at least four times a day for the first 24 hours.</td>
<td>No known antidotes or treatments.</td>
<td>Extravasation typically causes blue discoloration of the infusion site area and may require debridement and skin grafting (EMD Serono Inc., 2008). Assess the extravasation area for pain, blister formation, and skin sloughing periodically as needed or in accordance with institutional policy. In collaboration with the physician or advanced practice nurse, refer the patient for specialized care when indicated or needed (e.g., plastic or hand surgery consult, physical therapy, pain management, rehabilitation services).</td>
</tr>
<tr>
<td>Anthracyclines</td>
<td>Apply ice pack (but remove at least 15 minutes prior to dexrazoxane treatment).</td>
<td>Treatment: Dexrazoxane for injection (Biocodex Inc., 2011) Note: Totect® is the U.S. Food and Drug Administration (FDA)-approved treatment for anthracycline extravasation, and its manufacturer maintains a patent for use on the product. Although Zinecard® and generic dexrazoxane are neither indicated nor FDA-approved for anthracycline extravasation treatment, their clinical efficacy in treating anthracycline extravasations has been documented in the literature (Arroyo, Perez, Feijoo, &amp; Hernandez, 2010; Langer, 2007, 2008; Uges, Vollaard, Wilms, &amp; Brouwer, 2006). Mechanism of action: Unknown. Dose: The recommended dose of dexrazoxane is based on the patient’s body surface area: Day 1: 1,000 mg/m² Day 2: 1,000 mg/m² Day 3: 500 mg/m² The maximum recommended dose is 2,000 mg on days 1 and 2 and 1,000 mg on day 3. The dose should be reduced 50% in patients with creatinine clearance values less than 40 ml per minute. Preparation: Each 500 mg vial of dexrazoxane must be mixed with 50 ml diluent. The patient’s dose is then added to a 1,000 ml normal saline infusion bag for administration. Storage: Store at room temperature between 15°C–30°C (59°F–86°F).</td>
<td>The first dexrazoxane infusion should be initiated as soon as possible and within six hours of the anthracycline extravasation. Dexrazoxane should be infused over 1–2 hours in a large vein in an area other than the extravasation area (e.g., opposite arm). The same arm should be used only when the patient’s clinical status (e.g., lymphedema, loss of limb) precludes use of the unaffected arm, and a large vein distal to the extravasation site should be used for dexrazoxane administration. Dimethyl sulfoxide should not be applied to the extravasation area. Assess the extravasation area for pain, blister formation, and skin sloughing periodically as needed or in accordance with institutional policy. Instruct the patient to monitor the extravasation site and report fever, chills, blistering, skin sloughing, and worsening pain. Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness. Instruct the patient about treatment side effects (e.g., nausea and vomiting, diarrhea, stomatitis, bone marrow suppression, elevated liver enzyme levels, infusion-site burning). Monitor the patient’s complete blood count and liver enzyme levels.</td>
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(Continued on the next page)
**TABLE 2. Vesicant Extravasation Management Guidelines (Continued)**

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<tr>
<td>Antitumor antibiotics</td>
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<td>• Mitomycin</td>
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<tr>
<td>• Daclomycin (actinomycin D)</td>
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<tr>
<td><strong>Plant alkaloids and microtubule inhibitors</strong></td>
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</table>
| • Vinblastine                            | Apply warm pack for 15–20 minutes at least four times a day for the first 24 hours. | Antidote: Hyaluronidase  
Mechanism of action: Degrades hyaluronic acid and promotes drug dispersion and absorption  
Preparation: Available hyaluronidase preparations are  
• Amphotadase™ (bovine, hyaluronidase injection) (Amphastar Pharmaceuticals, 2005): Vial contains 150 units per 1 ml; use 1 ml of solution. Do not dilute. Use solution as provided. Store in refrigerator at 2°C–8°C (36°F–46°F).  
• Hylenex® (recombinant, hyaluronidase human injection) (Halozyme Therapeutics Inc., 2012): Vial contains 150 units per 1 ml. Do not dilute. Use solution as provided. Store in refrigerator at 2°C–8°C (36°F–46°F). | Administer 150 units of the hyaluronidase solution as five separate injections, each containing 0.2 ml of hyaluronidase, SC into the extravasation site using a 25-gauge or smaller needle (change needle with each injection). Assess the extravasation area for pain, blister formation, and skin sloughing periodically as needed or in accordance with institutional policy. Instruct the patient to monitor the extravasation site and report fever, chills, blistering, skin sloughing, and worsening pain. Instruct patients with peripheral extravasations to report arm or hand swelling and stiffness. |
| **Taxanes**                              | Apply ice pack for 15–20 minutes at least four times a day for the first 24 hours. | No known antidotes or treatments |                                                                         |
| • Docetaxel                              |                           |                       |                                                                         |
| • Paclitaxel                             |                           |                       |                                                                         |
| • Paclitaxel protein-bound particles for injectable suspension |                           |                       |                                                                         |

4. Remove the peripheral IV device or port needle.
5. Assess the site of the suspected extravasation.
6. Assess symptoms experienced by the patient (e.g., pain, impairment in range of motion of extremity).
7. Notify the physician or advanced practice nurse.
8. Initiate appropriate management measures in accordance with Table 2 and institutional policies.
   a) Anthracine extravasation antidotes and treatments
      1. Efficacy: The efficacy of extravasation antidotes and treatments is unknown, with the exception of dexrazoxane for injection, which has a 98% overall efficacy for treating anthracycline extravasation (Mouridsen et al., 2006). In two European studies, 53 of 54 patients with biopsy-confirmed anthracycline extravasation did not require surgical intervention after receiving dexrazoxane administered via IV daily for three days. The median baseline extravasation area was 25 cm² (range = 1–253 cm²), and 11 patients had extravasation areas exceeding 75 cm². Thirteen patients had late sequelae at the extravasation site such as pain, fibrosis, atrophy, and local sensory disturbance; all were mild (Mouridsen et al., 2006).
   b) Vesicant extravasation antidotes and treatments
      1. Efficacy: The efficacy of extravasation antidotes and treatments is unknown, with the exception of dexrazoxane for injection, which has a 98% overall efficacy for treating anthracycline extravasation (Mouridsen et al., 2006). In two European studies, 53 of 54 patients with biopsy-confirmed anthracycline extravasation did not require surgical intervention after receiving dexrazoxane administered via IV daily for three days. The median baseline extravasation area was 25 cm² (range = 1–253 cm²), and 11 patients had extravasation areas exceeding 75 cm². Thirteen patients had late sequelae at the extravasation site such as pain, fibrosis, atrophy, and local sensory disturbance; all were mild (Mouridsen et al., 2006).
2. Ancedotal reports: No clinical trials have been conducted to determine the efficacy of dimethyl sulfoxide, sodium thiosulfate, hyaluronidase, growth factors, early surgical intervention, saline washout or flush-out, or hyperbaric oxygen in treating biopsy-confirmed vesicant extravasations. Information about these antidotes and treatments is anecdotal and based on case reports (Dougherty & Oakley, 2011; Goolsby & Lombardo, 2006; Schrijvers, 2003; Wickham et al., 2006).

10. Documentation of vesicant extravasation and treatment. Extravasation treatments/antidotes used should also be documented.

11. Patient follow-up: Dependent on individual patient needs and institutional policies
   a) Periodically assess the patient’s response to extravasation treatment.
   b) Assessment may include inspection and measurement of the extravasation area, skin integrity, presence of pain or other symptoms, arm/hand mobility (for peripheral extravasations), and sensation.
   c) Obtain follow-up photographs that include the date and time in the photograph per institutional policy.
   d) In collaboration with the physician or advanced practice nurse, refer the patient for specialized care when indicated (e.g., plastic or hand surgery consultation, physical therapy, pain management, rehabilitation services).
   e) Instruct the patient to protect the extravasation area from sunlight, monitor the site, and report fever, chills, blistering, skin sloughing, and worsening pain.

References


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