Venous flare reaction, a localized allergic response associated with the administration of an irritant, is one of the most common chemotherapy infusion–related reactions. Etoposide, a drug commonly used in patients with lung cancer, has been reported to be an irritant with vesicant properties depending on the volume administered. This article presents the case of a patient who has a venous flare reaction immediately following the administration of etoposide for the treatment of diffuse large B-cell lymphoma. Managing such complications is crucial to maintaining patient safety. Proper training and education should be incorporated into nursing practice when identifying, preventing, and managing such reactions.

AT A GLANCE

- Etoposide is an irritant that is known to have vesicant properties in higher concentrations or larger volumes.
- One of the critical skills of a chemotherapy-competent oncology nurse is the ability to distinguish between extravasation and venous flare reaction.
- Evidence-based chemotherapy administration guidelines and institutional policies must guide nursing practice in the safe administration of chemotherapy.

KEYWORDS
etoposide; DLBCL; venous flare reaction; extravasation; chemotherapy

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Venous Flare Reactions

A case report of reactions following etoposide infusion

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This is a case of R.P., a 74-year-old man with stage IV diffuse large B-cell lymphoma (DLBCL), admitted for his second course of RICE chemotherapy (rituximab [Rituxan®], ifosfamide [Ifex®], carboplatin [Paraplatin®], and etoposide [Etopophos®]). At the time of initial diagnosis in 2008, DLBCL affected R.P.'s spleen, bone marrow, peripheral blood, and brain. He was treated for systemic and central nervous system (CNS) disease with R-CHOP (rituximab, cyclophosphamide [Cytoxan®], doxorubicin [Adriamycin®], vincristine [Oncovin®], and prednisone) and achieved complete remission in spring 2009. The lymphoma recurred in the brain, lung, and retroperitoneum in May 2017. He underwent six cycles of high-dose methotrexate (Trexall®), leucovorin (folinic acid) rescue, high-dose steroids, rituximab, and temozolomide (Temodar®). He then declined further treatment for asymptomatic systemic disease but agreed to undergo treatment for CNS disease. In December 2017, a magnetic resonance imaging of the brain showed complete resolution of CNS disease. Unfortunately, he had been found to have a new liver lesion the month before. The patient needed therapy again, and he was treated systemically with RICE chemotherapy. His first course of RICE chemotherapy was complicated by febrile neutropenia, which required an unplanned hospitalization and daily treatment with filgrastim (Neupogen®). During the second course of RICE chemotherapy, difficult venous access prompted a referral to establish a central vascular access device, which was firmly refused by the patient. Afterward, he developed a venous flare reaction, which was noticed only after the full dose of etoposide had been infused. The reaction resolved within an hour, with no further interventions. After the venous flare reaction, a healthcare professional discussed establishing a central vascular access device for subsequent infusions with the patient, who agreed.

Background

IV infusion is still the main modality of administering chemotherapy (Coyle, Griffie, & Czaplewski, 2014), even with an increase in the availability of oral agents. With the administration of these drugs comes the concern for infusion-related reactions. Two distinct infusion-related reactions consist of a venous flare reaction, which is an allergic local reaction, and extravasation, a more severe reaction ranging from skin erythema to soft tissue necrosis. Both infusion-related reactions may present with warmth, erythema, and pruritus. Extravasation can manifest as a more severe condition, presenting with pain at infusion site injection, blisters, and severe skin damage. Extravasation usually occurs with drugs known to be vesicants, which can cause tissue necrosis and blister formation because of leakage of chemotherapy from the blood vessel (Camp-Sorrell, 2018) (see Figure 1). A flare reaction occurs with inflammitants (St Luke's Cancer Alliance, 2015), drugs that cause transient mild

to moderate inflammation and painless skin erythema, resolving within one to two hours (European Oncology Nursing Society, 2007; Vogelzang, 1979).

In the case described, a venous flare reaction was observed following the completion of etoposide infusion (see Figure 2). R.P. received etoposide 80 mg/m² at 507.5 ml per hour for 60 minutes (the total volume was 507.5 ml when mixed with 500 ml sodium chloride; the total dose was rounded to 150 mg based on a body surface area of 1.88 m²). Several articles have identified etoposide as an irritant (Kreidieh, Moukadem, & El Saghir, 2016; Pérez Fidalgo et al., 2012). If extravasated, irritants have been known to cause irritation or inflammation at the extravasation site, without any blister formation. Highly concentrated etoposide that extravasates has been reported to have vesicant properties and cause severe tissue damage (Ener, Meglathery, & Styler, 2004; Kreidieh et al., 2016). R.P. presented with a painless erythematous streak along the involved vein, which remained asymptomatic. The reaction subsided spontaneously within an hour; as a result, no further intervention was performed. Figure 3 shows the necessary steps to manage venous flare reactions.

FIGURE 1.
MANAGEMENT OF EXTRAVASATION

- Stop infusion of chemotherapeutic agent.
- Aspirate extravasated drug with a syringe.
- Identify chemotherapeutic agent and administer an antidote if available.
- Remove vascular access device from patient and outline area of reaction.
- Take photograph of reaction site.
- Open extravasation kit.
- Notify provider.
- Nonpharmacologic management
  - Apply cold compress to site for 15–20 minutes 3–4 times per day for as many as 3 days.
  - Apply hydrocortisone 1% cream 2 times per day as long as redness persists.
  - Elevate limb to absorb extravasated agent.
  - Avoid tight clothing around affected arm.
  - Gently exercise the affected arm.
- Pharmacologic management
  - Use pain medication as needed and prescribed.
- Document incident.

Note. Based on information from Kreidieh et al., 2016; St Luke's Cancer Alliance, 2015.

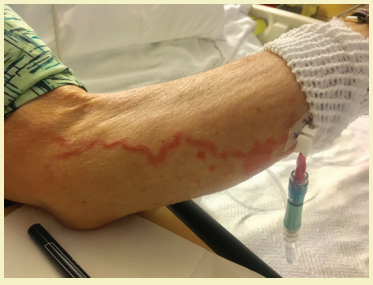
> "A venous flare reaction is distinguishable from extravasation by the absence of pain and presence of blood return from the IV."

Clinical Management and Treatment

Providing healthcare professionals with guidelines to safely administer chemotherapy remains an important element of safe clinical practice. In accordance with the 2016 American Society of Clinical Oncology (ASCO) and Oncology Nursing Society (ONS) chemotherapy administration guidelines, professionals have implemented safety standards to minimize risks associated with chemotherapy administration (Jacobson et al., 2009; Neuss et al., 2016).

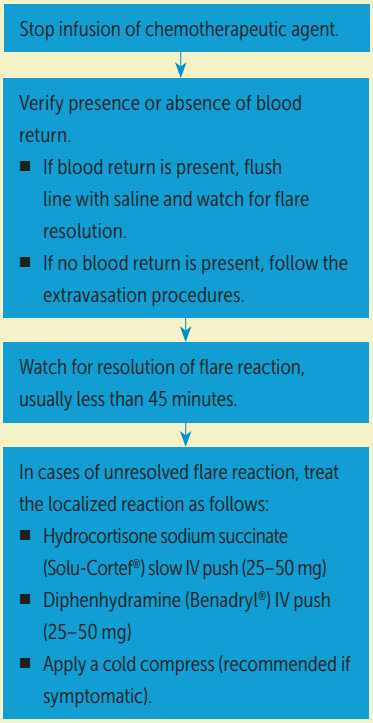
Training the oncology team to select an appropriate vascular access device (i.e., a central venous catheter or peripheral venous catheter) is critical. This includes inspecting and palpating veins to avoid use of fragile and previously used veins. Reviewing a patient's medical history can also help assess the appropriate vein to access (Kreidieh et al., 2016). In addition, understanding the mechanism of action of cytotoxic drugs and duration of treatment plays an important role in selecting the safest vascular access device (Schulmeister, 2010). The goal is to select the smallest cannula and needle to access the largest vein (Wengström & Margulies, 2008). Prior to administering chemotherapy, nurses and patients need to be educated on the prevention of IV complications associated with infusion and on recognition of early signs and symptoms

FIGURE 2.
VENOUS FLARE REACTION WITH ETOPOSIDE ADMINISTRATION



Note. Photo courtesy of Providence Health & Services, Southern California. Used with permission.

FIGURE 3.
MANAGEMENT OF VENOUS FLARE REACTIONS



Note. Based on information from Kreidieh et al., 2016; St Luke's Cancer Alliance, 2015; Twite et al., 2014.

of infusion-related reactions. Nurses should assess the catheter insertion site before, during, and after infusion, which includes monitoring the infusion site every 5–10 minutes (Coyle et al., 2014). For continuous infusions for 24 hours or longer, the catheter site needs to be assessed every 4 hours (Polovich, Olsen, & LeFebvre, 2014).

Key to the management of any infusion site reaction is stopping the IV infusion at the first sign of any infusion-related reaction (Polovich et al., 2014). Early recognition of symptoms and prompt initiation of treatment are crucial. Extravasation kits should be available at each respective unit, and nurses need to visually check the availability of extravasation kits prior to chemotherapy administration. The location of extravasation kits must be verified, and a thorough inspection of expiration dates for all antidotes that are included in the kit must be completed. A flare reaction is distinguishable from extravasation by the absence of pain and presence of blood return from the IV.

Conclusion

Recognizing infusion-related site reactions is critical to prevent harm to patients. ASCO and ONS have created guidelines for the management of such reactions. Evidence-based guidelines establish standards for patient care to ensure the safe administration of chemotherapy and proper management of chemotherapy reactions.

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