Anthracycline Extravasation: Reducing Risk and Improving Quality in the Community Setting

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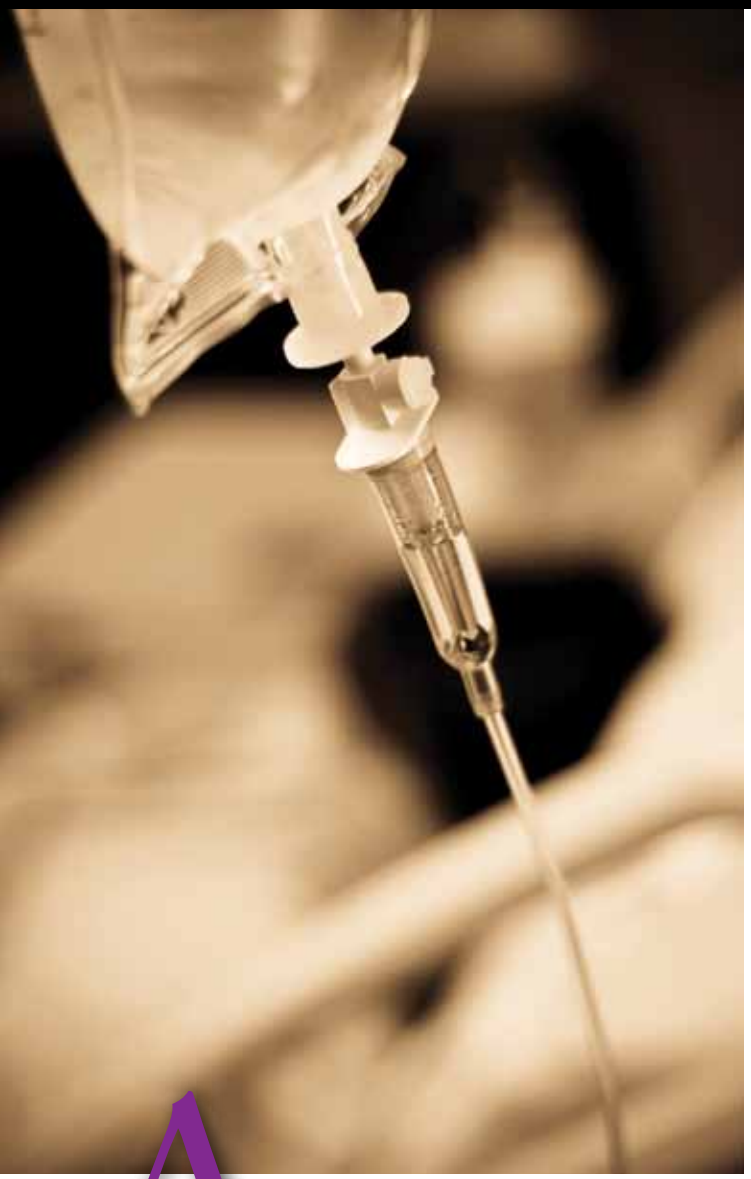

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Administering any infused drug is associated with a risk of accidental leakage, but the result of a chemotherapy extravasation can be particularly detrimental to a patient's medical outcome and quality of life. An extravasation occurs when a chemotherapeutic agent leaks out of a vein or central line into the surrounding tissues.[1] Extravasation during intravenous administration has been reported in 0.1 percent to 6.0 percent of patients.[2,3]

Patients with cancer receiving IV chemotherapy are considered to be particularly prone to extravasation because they tend to have thin, fragile, mobile veins requiring multiple punctures.[4] Drug concentrations are higher in small peripheral veins with low blood flow than in large veins with more rapid flow.[5] A nontoxic agent leaking into surrounding tissue is generally not problematic, but when a concentrated chemotherapeutic agent, such as anthracycline, leaks into surrounding tissue, severe tissue problems can result.

With anthracyclines, the incidence of extravasation has been estimated at 0.1 percent to 1.0 percent.[6] Although extravasation occurs infrequently, anthracycline extravasation can be extremely debilitating and disabling and requires immediate attention. Considered a workhorse in cancer treatment since the early 1970s,[7] anthracyclines are still widely used in treating many types of solid tumors and hematologic malignancies.[8] Anthracyclines have been the gold standard in treating breast cancer for nearly four decades. Table 1 on page 23 lists the types of anthracyclines and their use in oncology.

More than 500,000 doses of anthracyclines are administered intravenously each year in the United States.[9] Approximately 80 percent of anthracycline administrations are conducted in community cancer centers, which pose a unique challenge for these organizations spanning patient care, nursing protocols, and the financial and legal perspective.

Understanding Anthracycline Extravasation

The accidental leak of these vesicants can cause severe, lasting tissue damage and necrosis (localized death of living tissue).[1] When anthracyclines extravasate, they bind to DNA in cells of healthy tissue, where they cause cell death, and then spread to adjacent healthy cells. This process of cellular uptake of extracellular (i.e., from outside the cell) material creates a continuous cycle of tissue damage as the DNA-binding vesicant remains in the tissue for an extended period. The vesicant essentially "recirculates" in the surrounding healthy tissue and causes tissue injuries that become larger, deeper, and more painful over time.[10, 11]

The first sign of extravasation may be a burning sensation while the drug is being infused. The burning can be severe, and may persist for several minutes or hours, though it eventually diminishes. Over the next few weeks, the tissues surrounding the extravasation site may redden and become firm.[4] If the extravasation is small in size, the redness will gradually subside over the following weeks.[12, 13] However, if the extravasation is significant, a small necrotic area will form in the middle of the reddened, painful skin. In cases of painful necrosis, surgical debridement (the removal of damaged or infected tissue) is indicated.

If debridement is not performed, the necrosis can progress, resulting in a thick, leathery eschar (scab) surrounded by a band of red, painful skin. The underlying tendons and neurovascular structures (i.e., those pertaining to nerves

that control the caliber of blood vessels), particularly those on the back of the hand or at joints, may form the base of a painful, ulcerated lesion. The ulceration is often progressive, possibly leading to joint stiffness, nerve damage, and burning pain. These effects may be accompanied by loss of function of the involved extremity. The lesion may heal slowly or not at all, possibly resulting in a disability that may be long-term or even permanent.[4, 14]

In addition to the physical injury, extravasation can profoundly impact patients' emotional health and well-being. Most patients who experience extravasation become emotionally distressed at some point in the treatment process. Oftentimes, chemotherapy is suspended or delayed, leading some patients to worry that their cancer may recur while treatment is on hold. There have been reports of patients changing healthcare providers and pursuing legal action following a severe extravasation injury.

Anthracycline extravasation is preventable in most cases; however, extravasations can occur despite clinicians' best efforts. As nurses are responsible for anthracycline administration in most treatment settings, they can play a major role in preventing tissue injury resulting from extravasation. Nurses and other allied healthcare professionals must be knowledgeable about administering anthracycline chemotherapy, as well as the importance of extravasation prevention, detection, and management. Following an extravasation, prompt cooperation between nurses, pharmacists, and physicians is instrumental in successfully treating and managing an extravasation.

Risk-Reduction Strategies

Even when highly experienced professionals administer anthracycline, extravasations can happen. As noted above, the frequent use of anthracyclines by community cancer centers causes a liability risk. Thus, community cancer progams should be especially vigilant in reducing the risk of extravasations by adhering to extravasation policies, or developing an extravasation policy based on existing guidelines, such as those recently issued by the Oncology Nursing Society (ONS) and Infusion Nurses Society.

The first, and most important, approach in preventing or reducing the number of anthracycline extravasations is identifying patients who are at high risk for extravasations. When multiple risk factors are present, a greater likelihood of extravasation and severe injury exists. Here are four risk factors to consider.

Device-related risk factors. These include the use of metal needles or large-gauge catheters relative to vein size. Additionally, inadequately securing an IV needle or catheter or selecting an undesirable IV site location (e.g., back of the hand or wrist rather than the forearm, choosing the dominant hand) can also increase risk. Deeply implanting ports, especially in the abdominal area, can increase risk. Additional device-related risk factors include:

- Inappropriate needle length for the access device
- Development of a fibrin sheath (a thin, white adherent covering of tissue) at the tip of the catheter
- Separation, breakage, or dislodgement of a central venous catheter (a tube placed into a large vein in the neck, chest, or groin that is used to administer medication or obtain blood tests) or port.

Agent-related risk factors. These include vesicant potential, the volume of drug extravasated, and the administration schedule and frequency of IV chemotherapy, as the risk for extravasation increases with greater and more frequent dosing.

Patient-related risk factors. Age is the most common patient-related risk factor. Young patients may have difficulty communicating the key symptoms of extravasation. Similarly, older individuals may have communication problems due to the aging process or to heightened responses to medications for pain, nausea, or anxiety that have central nervous system effects. Older patients may also be combative if they suffer from dementia or other cognitive disorders. Patients who have other diseases may be at an increased risk of extravasation. Some of these include compromised circulation (such as with diabetes, Raynaud's syndrome, diseased lymph nodes, and malnutrition). For some patients, fear, anxiety, and cultural beliefs may interfere with their understanding of extravasation, as well as the speed with which they report problems.

Other patient-related risk factors include small size and poor condition of veins, multiple injection points, and patient activity (excessive moving during infusion).

Clinician-related risk factors. These include lack of knowledge of extravasation, inadequate IV skills, or lack of familiarity with central venous catheter use and management. Interruptions or distractions during drug administration can also raise the risk of tissue injury, as can procedural shortcuts. Nurses should be vigilant in monitoring patients who are receiving vesicant solutions, especially those administered over a short period of time.[15]

Case Study 1: Identifying At-Risk Patients

BK is a 69-year-old woman with T2N0M0 infiltrating lobular carcinoma in her left breast (ER+, PR+, HER 2-) being treated at a community hospital-based outpatient cancer center. The patient had a petite build (5'5"; 105 lbs.) and thin skin. She was scheduled to receive doxorubicin and immediately the staff identified her as an appropriate candidate for a port due to her build, vein access, and skin texture. Staff consulted with the patient and recommended she get a port implanted. However, she refused the procedure as she

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believed it was too invasive. Her husband accompanied her to her appointments.

Following her appointment at the cancer center, BK was administered doxorubicin via IV needle in her arm. Following center protocol, the nurse started the IV push of normal saline. Two ccs of doxorubicin were pushed, then the nurse pulled back to make sure she was still in the vein. After 8 mg of doxorubicin were administered, the nurse noticed a small hematoma forming. Based on the hematoma, the nurse deduced the catheter punctured the wall and leaked doxorubicin into the vessel wall, and the hematoma forming was doxorubicin accumulating between the vessel and the skin.

The nurse aspirated the needle and pulled back blood, indicating that her assumption was correct. She immediately consulted the oncologist and within an hour, a physician had initiated treatment of the extravasation with Totect® (dexrazoxane for injection), which is the only FDA-approved treatment for anthracycline extravasations. Fortunately, the patient had no lasting effects associated with anthracycline extravasation (tissue necrosis, flushing of the skin, muscle damage, and loss of function). The patient was able to continue treatment, but has since refused any type of infusion. She is still receiving radiation and tamoxifen.

This example of anthracycline extravasation occurred despite best practices. The patient was identified as high risk and refused the center's recommendation for a port. The nursing protocol and quick response facilitated the timely, and ultimately successful, management of an extravasation.

Evidence-based Management

For decades, much of the research on extravasation treatment has focused on anecdotal experiences. Some of these treatments can be found in Table 2 on page 23. The most common practices from 1976-2007 included early surgery with debridement, saline lavage and suction, and topical application of DSMO. Fortunately, a new option for the treatment of anthracycline extravasations exists today—Totect® (dexrazoxane for injection). Not only has Totect effected a dramatic change in the outcomes of patients treated for anthracycline extravasation influencing clinical practice, but the treatment has been included in the leading guidelines for oncology nurses on extravasation management.

In 2009 ONS made recommendations for the treatment of anthracycline extravasation in the third edition of *Chemotherapy and Biotherapy Guidelines and Recommendations for Practice*.[16] These guidelines recommend initial topical therapy by ice packs, which should be removed 15 minutes prior to Totect treatment. Totect should be initiated as soon as possible, and should be administered within a six-hour window. It will be infused over the course of three days for one to two hours each in a large peripheral vein away from the extravasation area. The ONS guidelines note that Totect has a 98 percent efficacy in "diminishing tissue damage," allowing for the continuation of chemotherapy. These guidelines also note that that the only biopsy-confirmed extravasation research was in clinical studies evaluating Totect.[17] The Infusion Nurses Society has also included Totect in its guidelines.

The 2007 FDA approval of Totect was based on two clinical studies. These studies demonstrated that when Totect was administered within six hours of the extravasation, 98.2 percent of patients did not require surgical intervention and 74 percent of patients saw no delay in chemotherapy treatment. Of all the patients, only one required surgery. Had Totect not been administered, Kane and others hypothesized that 10 to 25 percent of these patients would have required surgery.[18]

Case Study 2: Patient Counseling

PM is a 67-year-old patient with T2N0MX Grade 2 invasive ductal carcinoma (ER-, PR- HER2-). At 5'9" and 99 lbs., following lumpectomy with axillary node resection she had a venous access port implanted. PM was accompanied to this chemotherapy infusion appointment by her friend. The nurse administered saline, followed by the full dose of doxorubicin (122 mg). The patient then visited the restroom. When she came back, PM informed the nurse that her port did not "feel right" and she was experiencing burning and stinging. The nurse aspirated into the port and there was no blood return.

The patient underwent a chest X-ray, and it was discovered that the needle was out of the port; a dye study was not needed. It is unknown how much doxorubicin leaked into the chest cavity. Upon later reflection, the patient said she had experienced burning for some time before visiting the restroom, and felt some stinging while the nurse was pushing the doxorubicin.

Once the team confirmed that the needle was out, they initiated treatment with Totect working with the patient's physician. The patient experienced some swelling, but she had no sloughing, necrosis, or other ill effects. Fortunately, the patient was able to resume treatment on schedule, without needing to remove the port.

It is standard protocol at our community hospital-based outpatient cancer center to educate patients on anthracycline extravasations. When patients receive infusions, they often experience anxiety and concern. Some may believe that burning, swelling, or feeling cold is normal. Nurses should be trained to educate patients and counsel them in advance, before the infusion process can potentially distract patients. However rare, the possibility of having an anthracycline extravasation should be discussed with patients before every infusion. Working with a patient's

Table 1. Anthracyclines and Commonly Used Brand Names

Daunorubicin (Cerubidine®)
Doxorubicin (Adriamycin®)
Idarubicin (Idamycin®)
Epirubicin (Ellence®)

Table 2. Previous Treatment Options for Anthracycline Extravasations[1]

Topical cooling
Saline lavage and suction
Hyperbaric oxygen
Topical negative pressure
Administration or application of:
- Growth factors
- Free radical scavengers (e.g., dimethyl sulfoxide [DMSO])
- Ginkgo biloba extract
- Alpha-tocopherol
- Various pharmacologic agents

caregivers is also recommended, as they can bring a heightened awareness to the nursing staff if a patient observes symptoms. It is especially important during times when the average nurse-to-patient ratio is higher that patients know to speak up if they experience any changes during the infusion.

Working Beyond the Clinical Care Team

The two case studies demonstrate that despite multiple risk-reduction strategies and a highly experienced nursing staff, extravasations do occur. Given the frequency of anthracycline administrations in community cancer centers, it is important that risk-management policies are in place. Wickham advises that nurses prepare for extravasations as they do for other critical events, such as cardiac arrest.[15] She recommends having "mock extravasations" where members of the nursing staff, the oncologist, and the oncology pharmacist go through a simulated extravasation event in order to be better prepared to react in the patient's best interest.[15]

Our community hospital-based outpatient cancer center has established an extravasation management policy: stocking a kit of Totect, which is a full three-day treatment for anthracycline extravasation. This commitment to patient care is serious. If a kit is used, it is replaced within two days, working with a specialty pharmacy provider. During this time, the staff confirms that there are no anthracycline infusions scheduled, or reschedules infusions, to ensure a replacement Totect kit is onsite.

The upfront cost of stocking Totect is undoubtedly the biggest challenge community cancer centers will encounter. Our community hospital-based outpatient cancer center convened a team, including the clinical director, administrators, and the pharmacy and therapeutics (P&T) committee to review the risks of not stocking this extravasation antidote. Central to supporting a policy to stock Totect is its status as the only FDA-approved medication to treat extravasation. Our cancer center considers this policy clinically mandatory and legally prudent.

Additionally, Schulmeister and Camp-Sorrell recommend that cancer centers obtain patients' sign-off that document patient education and consultation on the risks of extravsations.[19] This practice can be an important measure in reducing plaintiffs in extravasation lawsuits.[19]

In conclusion, treatments with anthracycline present a risk to patients that cannot be fully mitigated. However, having educational and treatment tools at the ready will ensure the timely and effective management of anthracycline extravasations in the community cancer center.

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