FEATURE ARTICLE

Totect™: A New Agent for Treating Anthracycline Extravasation

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Anthracycline chemotherapy agents bind to DNA and cause cell death when they extravasate into healthy tissue. Although many approaches to managing extravasations have been studied and reported, data from two prospective clinical trials suggest that Totect™ (dexrazoxane for injection, TopoTarget USA, Inc.) is an effective anthracycline extravasation treatment. Only 1 of 54 patients with doxorubicin or epirubicin biopsy-confirmed extravasations treated with Totect developed tissue necrosis. Because nurses are on the forefront of extravasation prevention and management, they need to be knowledgeable about this new agent and how it is administered.

Extravasation of vesicant chemotherapy agents causes varying degrees of tissue damage and a variety of complications. The extent of damage is influenced by the type of vesicant that extravasates (e.g., DNA binding or nonbinding), the concentration and amount of the vesicant in the tissue, the location of the extravasation, and various patient factors. Vesicants that bind to nucleic acids in DNA (e.g., anthracyclines) bind to DNA in the cells of healthy tissue when they extravasate from the vein and promptly and directly cause cell death. DNA-anthracycline complexes released from dead cells in the tissue spread to adjacent healthy cells by endocytosis. This process of cellular uptake of extracellular substances creates a continuing cycle of tissue damage as the DNA-binding vesicant remains in the tissue for a prolonged period of time and is essentially "recirculated" in the surrounding healthy tissue (Luedke, Kennedy, & Rietschel, 1979; Mross, van der Vijgh, Gall, Boven, & Pinedo, 1988). Consequently, these extravasation injuries become larger in size, deeper in depth, and more painful over time.

Vesicants that do not bind to DNA (e.g., plant alkaloids) have an indirect rather than a direct effect on the cells in healthy tissue when they extravasate. Non–DNA-binding vesicants eventually are metabolized in the tissue and are neutralized more easily than DNA-binding agents (Ener, Meglathery, & Styler, 2004). This type of extravasation injury generally remains localized, is mildly to moderately painful, and improves on its own over time.

Vesicant extravasation injuries in areas of flexion, such as the wrist and elbow, or in areas with minimal overlying tissue, such as the dorsum of the hand and wrist, tend to be greater in their severity when compared to extravasation injuries in other areas, such as the forearm. Vesicant extravasations from deeply implanted ports may cause significant damage to the anterior chest wall and breast tissue (see Figure 1). Patient factors, such as older or very young age, comorbidity (e.g., diabetes), and immunosuppression, may influence the severity of extravasation injuries and patients' response to treatment of these injuries (Ener et al., 2004; Goolsby & Lombardo, 2006; Sauerland, Engelking, Wickham, & Corbi, 2006; Schulmeister & Camp-Sorrell, 2000).

Vesicant extravasations may cause partial- or full-thickness skin loss. Partial-thickness tissue injuries penetrate the epidermis and may extend into the dermis. The injuries often heal by epithelialization, whereby epithelial cells migrate from the wound edges to resurface the wound. The wounds usually are moist and painful

At a Glance

- Totect™ (dexrazoxane for injection, TopoTarget USA, Inc.) is indicated for the treatment of anthracycline extravasation.
- Totect is administered via IV daily for three days into a large vein that is not in or near the extravasation area. Topical cooling and other extravasation treatment (e.g., dimethyl sulfoxide) should not be used during treatment with Totect.
- Totect must be administered as soon as possible and within six hours of the anthracycline extravasation.

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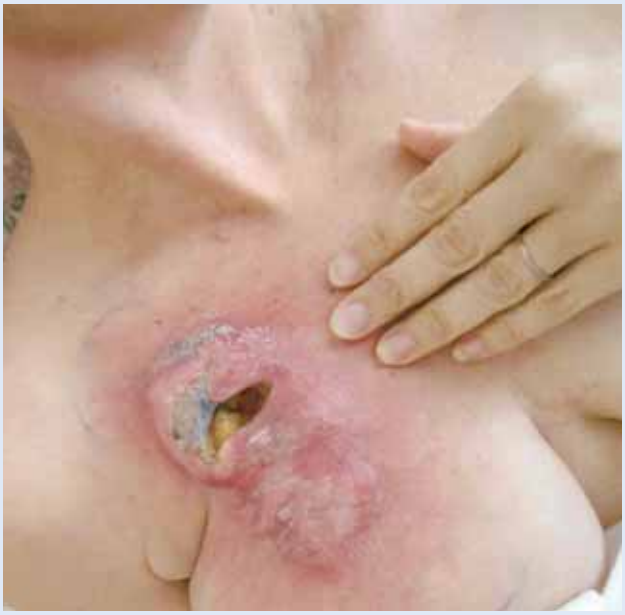

Figure 1. Doxorubicin Extravasation From a Port Implanted in the Subclavicular Area

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because of the loss of skin covering and exposure and irritation of nerve endings. Full-thickness tissue injuries extend beyond the dermis into the subcutaneous tissue. They may involve muscles, tendons, and sometimes bone and take longer to heal than partial-thickness tissue injuries. The wounds may heal by filling with granulation tissue, contraction, and epithelialization from the wound edges but may require surgical intervention (see Figure 2). Some patients have required extensive surgical debridement necessitating skin grafting or myocutaneous flap placement. In a few cases, vesicant extravasation has led to septicemia, permanent nerve loss, joint stiffness and contractures, and the development of compression syndrome (Ener et al., 2004; Schulmeister & Camp-Sorrell, 2000).

One aspect of vesicant extravasation management that has received little attention in the literature is the effect of extravasation injury on patients' emotional health and well-being. Most patients who experience an extensive extravasation injury become distressed at some point during extravasation treatment. In many cases, further chemotherapy treatment must be delayed. Some patients are worried that their cancer will recur or progress while their chemotherapy is on hold, which is a legitimate concern. In several cases, patients who experienced a severe extravasation injury changed healthcare providers and some pursued legal action (Schulmeister, 2005; Schulmeister & Camp-Sorrell, 2000).

The cost of treating extravasation injuries is unknown. Direct costs, such as those associated with multiple hospitalizations, home health care, physical therapy, and care provided by specialists (e.g., plastic surgeons), in one case were estimated to exceed $450,000 (Westlaw, 2006). Indirect costs, such as lost work revenue, payments for in-home assistance, and costs associated with traveling for specialized wound care, also may be significant.

Extravasation Management

In many cases, vesicant extravasation is preventable (Sauerland et al., 2006; Schrijvers, 2003). However, despite nurses' best efforts, extravasations sometimes occur. Nurses play a major role in preventive efforts because they are responsible for vesicant administration in most treatment settings. Nurses therefore must be knowledgeable about vesicant chemotherapy administration and extravasation prevention, detection, and management.

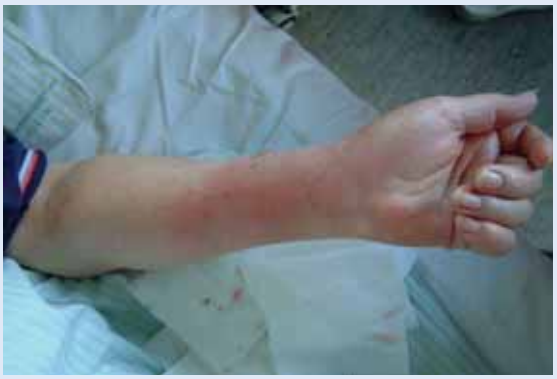
Vesicant extravasation management recently has been reviewed by several authors (Ener et al., 2004; Goolsby & Lombardo, 2006; Schrijvers, 2003; Wickham, Engelking, Sauerland, & Corbi, 2006). The literature that forms the basis of the reviews is mostly comprised of anecdotal reports and small clinical study findings; consequently, evidence is lacking to guide extravasation management. As noted by Wickham et al., "Most suggestions to use local comfort measures, local antidotes, debridement, or other surgical interventions remain empirical and controversial" (p. 1143).

Anthracycline Extravasation

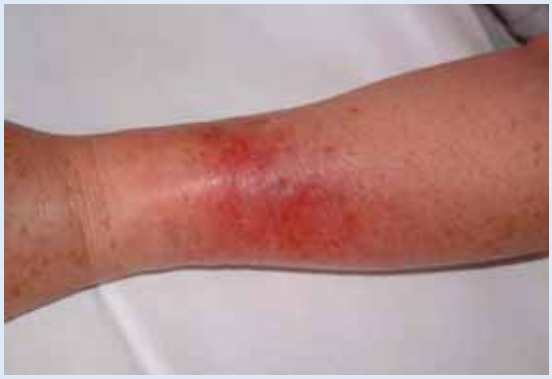
Although extravasation of any vesicant has the potential to cause tissue damage, anthracycline extravasations seem to have the most potential to cause severe damage. Case reports of doxorubicin extravasation injuries were first reported in 1976 (Rudolph, Stein, & Pattillo, 1976). At that time, doxorubicin typically was administered via steel winged ("butterfly") needles inserted into peripheral veins, often in the dorsum of the hand. Early reports noted that doxorubicin infiltration into subcutaneous tissues caused "ulcers filled with shaggy necrotic yellowish debris" (Rudolph et al., p. 1093), which often were accompanied by an intense local inflammatory response that progressed to full-thickness skin loss and irreversible damage to underlying tendons and neurovascular structures (Reilly, Neifeld, & Rosenberg, 1977). In 1978, Bowers and Lynch observed that doxorubicin extravasation injuries "develop at a slow rate, continue to increase in severity for several weeks, and do not heal in the usual manner" (p. 86).

Additional case reports documented that spontaneous healing rarely occurred and surgical excision of the involved tissues usually was required (Barden, 1980; Mehta & Najar, 1978; Reilly et al., 1977). Split-thickness skin grafting often was needed as well, especially if tissue necrosis extended down to the extensor tendons of the hands. The periosteum overlying the metacarpals frequently was involved, which presented a treatment dilemma because a skin graft is unable to survive on bare cortical bone. In those instances, pedicle skin flaps were required to cover the area of injury (Bowers & Lynch, 1978; Laughlin, Landeen, & Habal, 1979).

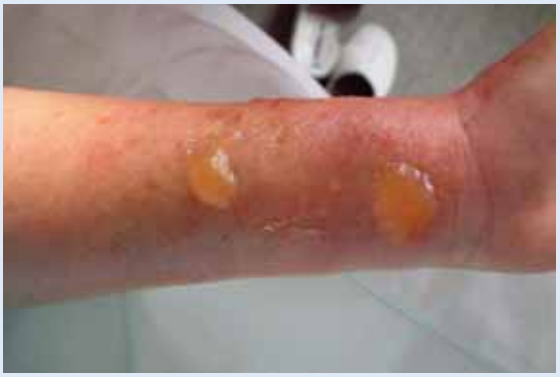
Since the late 1970s, researchers have studied various treatments and antidotes for managing anthracycline extravasations and clinicians have reported their anecdotal experiences with various treatment modalities. Treatments that have been studied or reported include topical cooling, saline lavage and suction, hyperbaric oxygen, topical negative pressure, and administration or application of growth factors, free radical scavengers (e.g., dimethyl sulfoxide [DMSO], ginkgo biloba extract, alpha-tocopherol), and various pharmacologic agents. Current



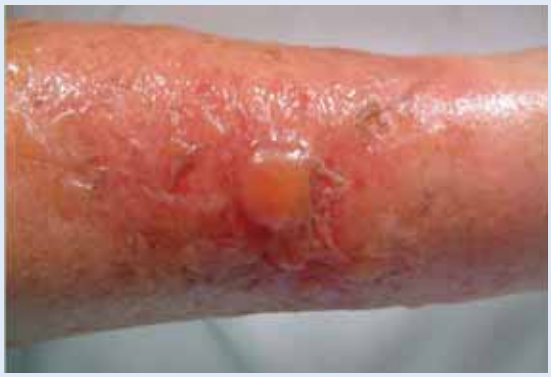
Day 1: Extravasation area is red and painful.



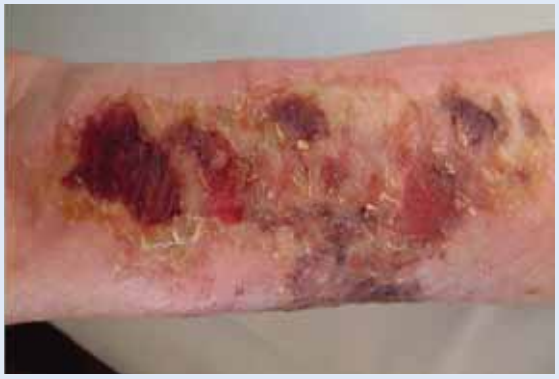
Day 4: Redness and swelling worsen.



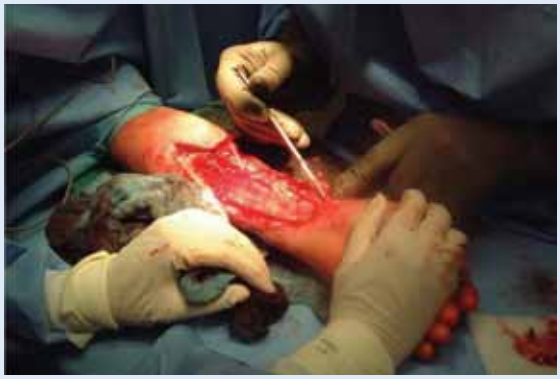
Day 8: Blisters develop.



Day 10: Blistering continues, and peeling begins to occur.



Day 12: The patient's arm is indurated, and tissue necrosis is apparent.



Surgical debridement is performed to remove the necrotic tissue.

A skin graft is applied to cover the area.

The patient's forearm is permanently disfigured.

Figure 2. Doxorubicin Extravasation in a Patient's Forearm That Progressed Over Time

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practice for managing anthracycline extravasation varies; from 1976–2007, early surgery with debridement, saline lavage and suction, and topical application of DMSO reportedly have been used more often than other treatments. Topical cooling with ice is recommended and frequently used as an initial treatment for anthracycline extravasation (Ener et al., 2004; Goolsby & Lombardo, 2006; Schrijvers; 2003; Wickham et al., 2006).

Antidotes and Treatments

Much of the research on anthracycline extravasation treatment has focused on the efficacy of antidotes. In an early study, local injections of alpha-tocopherol (vitamin E), cimetidine, diphenhydramine, heparin, hyaluronidase, lidocaine, and N-acetylcysteine were found to be ineffective in reducing doxorubicin-induced ulceration in mice. Two opposing beta-adrenergic compounds, the antagonist propranolol and agonist isoproterenol reduced but did not prevent ulceration, suggesting that the beta-adrenergic receptor played a role in mediating doxorubicin-induced tissue necrosis (Dorr & Alberts, 1981). When alpha-tocopherol, amifostine, merbarone (a catalytic inhibitor of topoisomerase II), aclarubicin (an antitumor antibiotic), ethylenediamine tetra-acetic acid (a chelating agent), dexrazoxane, and ADR-925 (a product of dexrazoxane hydrolysis) were studied as antidotes for doxorubicin extravasation injuries in mice, only dexrazoxane was found to be effective in preventing tissue necrosis (Langer, Sehested, & Jensen, 2001).

Dexrazoxane is a metal ion chelator that protects against the free radical toxicity induced by formation of anthracycline-iron complexes. Dexrazoxane is believed to provide protection from free radical damage by binding and thus concealing iron from oxygen. Another proposed mechanism of action is that it is a catalytic inhibitor; anthracyclines increase levels of topoisomerase II–mediated cleavage, which cause DNA strand breaks (Andoh & Ishida, 1998; Hellmann, 1998). Dexrazoxane's activity in protecting tissue from anthracycline extravasation–induced injury may be because of its ability to scavenge free radicals, its effect on the catalytic cycle of topoisomerase II, a combined effect, or additional mechanisms (Langer et al., 2000a).

When mice were subcutaneously injected with 2 mg/kg of doxorubicin and treated with varying doses of dexrazoxane (125, 250, or 375 mg/kg) at varying times (concurrent with doxorubicin or three or six hours afterward), concurrent dexrazoxane treatment reduced the number of mice with wounds from 88% to 21% (Langer et al., 1999). In another study, mice were injected with the anthracyclines daunorubicin, doxorubicin, and idarubicin and various doses of dexrazoxane were either infused via IV or injected into the intraperitoneal space at various times (immediately following, three or six hours later, or on days 1 and 2). Significant reduction in ulcer frequency, size, and duration was observed when dexrazoxane was administered up to six hours after injection. Triple treatment (administered at the time of anthracycline injection and repeated three and six hours later) prevented ulcers from occurring. The results led to the following clinical practice changes at the researchers' hospital (National University Hospital, Copenhagen, Denmark): (a) Administration of anthracyclines via a central venous access device now is optional rather than mandatory, and (b) anthracycline extravasations are treated with prompt surgical evaluation, and dexrazoxane 1,000 mg/m^2 IV is administered within six hours of the extravasation and repeated on day 2. On day 3, a dexrazoxane dose of 500 mg/m^2 is given (Langer et al., 2000b).

In 2000, Langer, Sehested, Jensen, Buter, and Giaccone published a letter to the editor in the *Journal of Clinical Oncology* in which they described the efficacy of dexrazoxane in treating two anthracycline extravasations. A woman with breast cancer experienced an extravasation of an estimated doxorubicin dose of 149 mg, which occurred as a result of needle displacement from an implanted port, and was treated with the dexrazoxane protocol previously mentioned. A second patient with breast cancer had a 7 x 11 cm epirubicin extravasation (verified by fluorescence microscopy, which confirms that an extravasation did occur) in her forearm and was treated with dexrazoxane. Tissue necrosis did not develop in either patient, and both were able to resume chemotherapy after a one-week delay. Both patients experienced mild leukopenia (Common Toxicity Criteria grade 2) and transient elevation of liver transaminases (twice the upper limit of normal for < 7 days). No sequelae were observed at the three-month follow-up examinations of the patients (Langer et al., 2000). In 2003, oncologists in Lebanon reported that they treated a 50 mg doxorubicin extravasation from an implanted port in accordance with the protocol proposed by Langer et al. (2000b). They also topically applied DMSO on the skin every six hours for three doses and did not apply cold compresses to avoid vasoconstriction and allow the dexrazoxane to diffuse freely in the injured area. Four months following the extravasation injury, the patient had a 2 mm dehiscence of the surgical scar overlying her port that healed a month later. The oncologists concluded that dexrazoxane prevented the development of severe tissue necrosis (El-Saghir et al., 2003).

In a case report from Denmark, dexrazoxane was used to treat an epirubicin extravasation that occurred in the forearm of a 41-year-old woman with breast cancer. The dose of epirubicin suspected to have extravasated was not stated. A 4 x 6 cm area of redness and swelling developed and three of five biopsy specimens taken from the area were fluorescent, verifying that an epirubicin extravasation occurred. Twenty-four hours after dexrazoxane treatment was initiated, the area was free of erythema and the patient no longer experienced pain. She did not develop tissue necrosis, and the only sequela of dexrazoxane treatment was slight numbness around the extravasation area. The patient also was able to continue adjuvant chemotherapy as planned (Jensen, Lock-Andersen, Langer, & Mejer, 2003).

In Germany, approximately 20 mg of a 30 mg dose of doxorubicin extravasated from a vein in the forearm of a woman being treated for metastatic breast cancer. Dexrazoxane was administered for three days (1,500 mg on days 1 and 2, 750 mg on day 3) and DMSO 99% was applied topically for five days. Erythema, swelling, and pain at the extravasation site gradually diminished, tissue necrosis did not develop, and the patient's next course of chemotherapy was able to be administered on schedule the following week. An estimated 20 mg of a prodrug of doxorubicin, which possesses an extravasation potential similar to that of doxorubicin, extravasated in the forearm of a man with oropharyngeal cancer. The patient was treated using the same protocol that was used to treat the woman with metastatic breast cancer described previously. No tissue

necrosis occurred, and the patient was able to receive further chemotherapy on schedule three weeks later (Frost, Gmehling, Azemar, Unger, & Mross, 2006).

Although DMSO was applied concurrently to the extravasations that were reported in Germany and did not appear to impact the clinical efficacy of dexrazoxane, the addition of topical DMSO reduced the efficacy of dexrazoxane in an animal study conducted in Demark. Seventy-two mice were treated with dexrazoxane, topical DMSO, and subcutaneous hydrocortisone as single agents and in combination with one another. Dexrazoxane completely prevented tissue necrosis, and neither DMSO nor hydrocortisone prevented necrosis. Concurrent administration of DMSO with dexrazoxane was not as effective in preventing tissue necrosis as dexrazoxane alone. The researchers concluded that dexrazoxane works most effectively as a single agent in the treatment of anthracycline extravasations (Langer, Thougaard, Sehested, & Jensen, 2006).

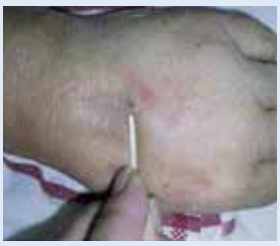
From July 2001–August 2005, 79 patients with 80 peripheral anthracycline extravasations were enrolled in two prospective, open-label clinical trials of dexrazoxane (one patient had two extravasations occur in an eight-day period). The first study enrolled patients from 10 cancer centers in Denmark, and the second study enrolled patients from 24 centers in Denmark, Germany, Italy, and the Netherlands. Anthracycline extravasation was verified by fluorescence microscopy of patients' tissue biopsies. Fifty-four patients were evaluable; 13 of the 25 patients who could not be evaluated had negative biopsies (which indicate that although an extravasation was suspected, it did not occur), 4 did not have biopsies performed, and 8 others were excluded for protocol violations, cases that could not be reviewed, patients who received concurrent treatment, and late enrollments in the study. Patients ranged in age from 34–81 years (mean = 56 years). Seventeen of the patients were male (31%), and 37 were female (69%). The most common cancer diagnosis among the patients was breast cancer (50%), followed by lymphoma (39%), and other types of cancer (9%). Patients experienced extravasations of doxorubicin (n = 23) or epirubicin (n = 31). The mean extravasation area was 23.6 cm^2 in the first study and 39 cm^2 in the second study. Eleven patients had areas of extravasation exceeding 75 cm^2. Symptoms experienced by the patients in both studies are listed in Table 1. All patients received dexrazoxane for three consecutive days, with a dose of 1,000 mg/m^2 on days 1 and 2 and a dose of 500 mg/m^2 on day 3. None of the 18 evaluable patients in the first study and only one of the 36 evaluable patients in the second study had tissue necrosis occur (overall efficacy = 98%). A doxorubicin extravasation prior to and following dexrazoxane treatment is shown in Figure 3. In the clinical trial studies, the patient who developed tissue necrosis had a very large area of doxorubicin extravasation measuring 253 cm^2. Tissue necrosis began to occur nine days following the extravasation and was surgically excised. Most of the patients (71%) were able to receive further chemotherapy treatment on schedule. Treatment sequelae included mild pain (19%) and mild sensory disturbances (17%) at the extravasation site (Giaccone, 2006; P. Knoblauch, December 22, 2006, personal communication; Mouridsen et al., 2006a, 2006b). Marketing authorization of dexrazoxane (Savene™, TopoTarget A/S) as a treatment for anthracycline extravasation in Europe received European Commission approval in July 2006. Totect™ (TopoTarget USA, Inc.) received U.S. Food and Drug Administration approval in May 2007.

Table 1. Baseline Symptoms of Patients Experiencing Anthracycline Extravasations

SYMPTOM	n	%
Swelling	45	83
Redness	42	78
Pain	23	43
Blistering	2	4
Numbness	2	4

N = 54

Note. Based on information from Giaccone, 2006.



Before treatment, the patient experiences erythema and swelling around the infusion site.

After treatment, the small scars represent the locations of punch biopsies used to confirm the tissue extravasation.

Figure 3. Doxorubicin Extravasation on the Dorsum of a Patient's Left Hand Before and After Dexrazoxane Treatment

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Totect Administration

Totect is indicated for the treatment of anthracycline extravasation. It is packaged in a kit that contains 10 vials of Totect powder and 10 vials of Totect diluent solution. Each vial of Totect powder contains 500 mg of dexrazoxane hydrochloride. After reconstitution with Totect diluent, supplied in the kit in 50 ml vials, the concentration of Totect is 10 mg/ml. Totect is administered once daily for three consecutive days. The first infusion needs to be initiated as soon as possible and within six hours of the anthracycline extravasation. The patient's body surface area is used to calculate the dose of Totect, and a single dose of Totect should not exceed 2,000 mg. The dose of the first infusion (day 1) is 1,000 mg/m^2. On day 2, as close as possible to 24 hours following the time the day 1 dose was given, a second dose of 1,000 mg/m^2 is administered. On day 3, a dose of 500 mg/m^2 is given. The Totect dose should be reduced 50% in patients with creatinine clearance values less than 40 ml per minute. Totect has a biphasic elimination; the mean initial elimination half-life is approximately 30 minutes, and the mean terminal elimination half-life is 2.8 hours. In in

- Totect™ is indicated for the treatment of anthracycline extravasation (e.g., doxorubicin, daunorubicin, epirubicin, idarubicin).
- Institutional guidelines for safe handling of cytotoxic substances should be followed when preparing, administering, storing, and disposing of Totect. The use of gloves is recommended. If Totect powder, Totect diluent, or the mixed solution comes in contact with the skin or mucosa, the area should be washed thoroughly with soap and water.
- Totect powder must be reconstituted with supplied Totect diluent to provide a concentration of 10 mg/ml. The reconstituted solution has a slight yellow color. The patient's dose of Totect (based on body surface area) is diluted in 1,000 ml of 0.9% normal saline (NaCl).
- The recommended dose of Totect is

  Day 1: 1,000 mg/m^2

  Day 2: 1,000 mg/m^2

  Day 3: 500 mg/m^2
- A maximum single dose should not exceed 2,000 mg. Patients with a body surface area of more than 2 m^2 should receive a dose of 2,000 mg on days 1 and 2 and 1,000 mg on day 3.
- The Totect dose should be reduced 50% in patients with creatinine clearance values less than 40 ml per minute.
- The first infusion of Totect should be administered as soon as possible and within the first six hours after the extravasation.
- Topical cooling, such as ice packs, should be removed for at least 15 minutes prior to and during Totect administration.
- Concurrent extravasation treatment, such as topical dimethyl sulfoxide application, should not be used in conjunction with Totect; if administered, they may worsen extravasation-induced tissue injury.
- Totect is administered as an IV infusion over one to two hours into a large vein in an area or extremity other than the one affected by the extravasation.
- Totect administration on days 2 and 3 should begin as close to 24 and 48 hours after the time of the day 1 infusion (e.g., if the day 1 infusion was initiated at noon, then the day 2 infusion should begin at noon on the following day, and the day 3 infusion should begin at noon on the third day).
- Totect treatment is associated with neutropenia and thrombocytopenia. The patient's complete blood count should be monitored.
- Unopened vials of Totect powder and Totect diluent should be stored at room temperature and protected from light and heat.
- Totect should be reconstituted, diluted, and used immediately. It is stable for four hours when refrigerated.
- It is not known whether Totect or its metabolities are excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in breastfed infants, a decision must be made to to discontinue breastfeeding or discontinue the drug, taking into account the importance of the drug to the mother.
- Totect is not recommended for use in children because of the lack of efficacy and safety data in this population.
- Reversible elevations of liver enzymes may occur with Totect treatment. Liver enzyme levels should be monitored.
- The most common side effects of Totect are neutropenia, thrombocytopenia, fever, infusion site reactions (e.g., pain, phlebitis), and nausea and vomiting.

Figure 4. Totect™ Dosing and Administration Guidelines

Note. Based on information from TopoTarget USA, Inc., 2007.

vitro studies, none of the five major cytochrome P450 isoenzymes was inhibited by Totect, which suggests that significant metabolism via this cytochrome is not likely. Detailed administration guidelines are described in Figure 4 (TopoTarget USA, Inc., 2007).

Totect is only effective for treating anthracycline extravasation. It is not effective, nor indicated, for treating other types of extravasations, such as extravasation of plant alkaloids (e.g., vinblastine, vincristine, vinorelbine), taxanes (e.g., paclitaxel, docetaxel), or alkalating agents (e.g., mechlorethamine [commonly known as nitrogen mustard], platinum analogs).

Implications for Practice

Nurses are integral in preventing and managing anthracycline extravasation. They usually are the first to detect that an extravasation may have occurred and need to be well informed about how to best proceed once an extravasation has been identified. With the introduction of Totect, healthcare providers have yet another option for treating anthracycline extravasations.

Although the efficacy data are compelling, both of the clinical trials of the agent were conducted on patients with peripheral anthracycline extravasations. In the published clinical trials report, none of the evaluable patients in either trial had an extravasation from an implanted port or central venous catheter (CVC) (Mouridsen et al., 2006b). Published data on response in patients with extravasations from implanted ports are limited to two case reports. As noted previously, neither patient developed tissue necrosis (El-Saghir et al., 2003; Langer et al., 2000).

Nurses will be instrumental in collecting further data about the efficacy of Totect, especially in patients with extravasations from implanted ports or CVCs. Nurses also need to be familiar with this new agent and able to respond to questions they may be asked about it (see Figure 5). Because Totect is a nurse-administered treatment, nurses have an instrumental role in ensuring that it is given safely and correctly. Totect must be administered as soon as possible and within six hours following the extravasation. Totect is an IV treatment; therefore, in most cases, nurses will insert an IV device to administer the agent. Nurses also need to check the expiration date (Totect is an agent that hopefully will rarely—or never—be used) and calculate or verify the doses of Totect that need to be administered daily for three days. Depending on the institution, nurses may be responsible for reconstituting and preparing Totect in addition to administering it or may need to develop policies and procedures with pharmacy staff to ensure that Totect is promptly prepared and the first dose is administered within six hours of extravasation. Nurses also need to teach patients about Totect and monitor response to treatment. Lastly, nurses must document the extravasation and its management and coordinate patient follow-up.

Nurses must continue to administer anthracyclines with great care. The availability of Totect to treat anthracycline extravasation does not negate the need for extravasation prevention efforts. When confronted by situations in which the placement or patency of an IV device is questionable, nurses should not proceed with anthracycline chemotherapy simply because an extravasation treatment is available. In addition, patient monitoring should not be any less vigilant. Instead, nurses need to

What is the best course of action to take when it is suspected but uncertain that an anthracycline extravasation has occurred? Is Totect administration warranted?

Clinical signs and symptoms of an anthracycline extravasation include swelling, a stinging or burning sensation (usually, but not always), loss of blood return from the IV device, and an IV flow rate that slows or stops (Polovich et al., 2005). If any of these signs or symptoms occur, the nurse should immediately stop administering the anthracycline and assess the patient and the patient's IV device. Because anthracycline extravasations have a high propensity to cause tissue necrosis, when in doubt, it is better to err on the side of caution and presume that an extravasation has occurred (Ener et al., 2004). In these instances, Totect administration is warranted.

Is Totect appropriate for the treatment of small anthracycline extravasations? Do guidelines exist regarding how large or severe an extravasation needs to be to justify the expense of Totect (e.g., drug and supply costs, drug administration and facility fees, patient's and nurse's time)?

Jenkins and Corden (1983), researchers at the National Cancer Institute, conducted studies to determine the vesicant activity of chemotherapeutic agents and observed that doxorubicin and dactinomycin ranked highest in what they termed "ulcerogenic propensity." Depending on their location and other factors, even small anthracycline extravasations have the potential to cause significant tissue damage; therefore, Totect is indicated for the treatment of **any** anthracycline extravasation, regardless of size.

How does Totect differ from generic dexrazoxane and Zinecard® ([Pfizer, Inc.] also marketed in 28 countries other than the United States as Cardioxane® [Chiron Corporation])?

The major differences between Totect and generic dexrazoxane and Zinecard are their indications and packaging. Totect is indicated for the treatment of anthracycline extravasations, whereas generic dexrazoxane and Zinecard are indicated for reducing doxorubicin-induced cardiomyopathy in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m^2. Generic dexrazoxane and Zinecard are available in 250 mg and 500 mg vials. Totect is packaged specifically for extravasation treatment and is supplied in 500 mg vials. The Totect kit contains 10 vials of Totect powder and 10 vials of Totect diluent packaged together to provide a complete three-day anthracycline extravasation treatment. TopoTarget also has a U.S. patent for the use of Totect for extravasation treatment; substitution of any other form of dexrazoxane for Totect anthracycline extravasation treatment constitutes patent infringement (Bedford Laboratories, 2006; Pfizer, Inc., 2000; TopoTarget USA, Inc., 2006).

What should be done if two vesicants extravasate (e.g., an anthracycline vesicant such as doxorubicin and another vesicant such as vincristine, a plant alkaloid)?

A few chemotherapy treatment protocols contain two vesicants with extravasation potential, such as doxorubicin and vincristine. When both vesicants are suspected to have extravasated, a clinical dilemma arises because the vesicants have different antidotes and opposite physical treatment (topical cooling is recommended for doxorubicin extravastion whereas heat is recommended for vincristine extravasation) (Polovich et al., 2005). Authors of a case report of a doxorubicin and vincristine extravasation recommended that the area should not be heated or cooled (Comas & Mateu, 1996), which is a reasonable action to take. Totect also should be considered (P. Knoblauch, December 22, 2006, personal communication) because doxorubicin is a DNA-binding agent with great potential to cause tissue necrosis. Conversely, vincristine does not bind to DNA, is eventually metabolized in the tissue, and does not cause the degree of tissue necrosis that commonly is observed with DNA-binding agents (Ener et al., 2004).

Is Totect indicated in the treatment of extravasation of liposomal formulations of anthracyclines?

Liposomal formulations of anthracyclines have a phospholipid bilayer that encapsulates the active drug. They have a longer elimination half-life and a different toxicity profile than nonliposomal formulations of anthracyclines (Di Paolo, 2004). The manufacturers of doxorubicin hydrochloride liposome (Doxil®, Ortho Biotech) and liposomal daunorubicin (DaunoXome®, Gilead Sciences, Inc.) classify these agents as irritants and advise using precautions to avoid extravasation. In published case reports, skin toxicity following extravasation of liposomal anthracyclines was limited to skin discoloration and decreased sensation. Tissue necrosis did not occur (Cabriales et al., 1998; Lokich, 1999). Extravasation of liposomal anthracyclines should be managed symptomatically; Totect is not indicated (P. Knoblauch, December 22, 2006, personal communication).

Is it sufficient to have one Totect kit per treatment facility?

In busy treatment facilities, two or more Totect kits should be available in the unlikely event that multiple anthracycline extravasations occur within hours or days of one another (receiving a replacement kit generally takes a few days). In some settings, a centrally located kit may be feasible to have available; for instance, a clinic with satellite offices may elect to keep one Totect kit at its main office. (Keep in mind that Totect administration needs to be initiated within six hours of the extravasation, so travel time must be considered. Also, someone in the satellite office must be able to leave the office to pick up the Totect kit or some other transportation arrangement must be made.) In some communities, cancer treatment facilities may want to consider partnering with other facilities to make their Totect kits available as "back-up" kits when a kit is used at one of the facilities.

What are Totect purchasing considerations?

A Totect anthracycline extravasation treatment kit is not a recurring expense. A new kit is purchased when a kit has been used or the drug has reached its expiration date. Additional information about Totect, including ordering, coding, and billing, can be found on the Totect Web site at www.TopoTarget.com or by calling 866-470-8274.

Figure 5. Questions and Answers About Anthracycline Extravasation Management and the Role of Totect™

continue to use due diligence when administering anthracyclines (and all other vesicants) and monitoring patients receiving vesicant chemotherapy.

Summary

Vesicant extravasations are best prevented; however, prevention is not always possible. Anthracycline extravasations historically have been, for the most part, managed by topical cooling and a variety of other measures, such as early surgery, saline lavage, and DMSO application. Unfortunately, none of these measures has clearly demonstrated efficacy. Totect, introduced in 2007, is packaged as an extravasation management kit. Clinical trial data support the efficacy of Totect as an anthracycline extravasation treatment. Nurses need to be aware of this new treatment and prepared to safely administer it if an anthracycline extravasation inadvertently occurs.

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