Dexrazoxane (Totect™): FDA Review and Approval for the Treatment of Accidental Extravasation Following Intravenous Anthracycline Chemotherapy

ROBERT C. KANE, W. DAVID McGUINN JR., RAMZI DAGHER, ROBERT JUSTICE, RICHARD PAZDUR

Office of Oncology Drug Products, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, Maryland, USA

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LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Evaluate anthracycline tissue injury resulting from drug extravasation.
3. Describe the proposed mechanism of action of dexrazoxane for this use.

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ABSTRACT

Management of anthracycline extravasation is problematic and most reports are anecdotal. On September 6, 2007, the U.S. Food and Drug Administration approved Totect™ 500 mg (dexrazoxane hydrochloride for injection) for the treatment of extravasation resulting from i.v. anthracycline chemotherapy. In two studies, a total of 57 evaluable patients experienced extravasation from peripheral vein or central venous access sites with local swelling, pain, or redness. The presence of anthracycline in skin biopsy tissue was confirmed by tissue fluorescence, and treatment with a 3-day schedule of dexrazoxane began within 6 hours of the event. The primary endpoint was a reduction in the need for surgical intervention. Only one patient required surgical repair of the injury site, and late sequelae in the remainder were absent or mild. Also, the sponsor, TopoTarget A/S, Copenhagen, Denmark, performed controlled nonclinical studies in support of dexrazoxane dose and timing for the reduction of tissue injury resulting from anthracycline extravasation. For this uncommon but serious complication of anthracycline therapy, the need for surgical intervention was 1.7% with this regimen. The Oncologist 2008; 13:445–450.
INTRODUCTION
On September 6, 2007, the U.S. Food and Drug Administration (FDA) approved Totect™ 500 mg (dexrazoxane for injection; TopoTarget A/S, Copenhagen, Denmark) for the treatment of extravasation resulting from i.v. anthracycline chemotherapy (Fig. 1) [1]. The sponsor, TopoTarget A/S, obtained a U.S. patent for a new method of use for the marketed drug, dexrazoxane, to treat anthracycline extravasation injury and conducted two efficacy studies in Europe to evaluate its use as a postextravasation treatment. In each study, the observed frequency and severity of tissue damage appeared to be reduced by dexrazoxane infusions given after anthracycline extravasation.

Accidental extravasation of i.v. anthracycline chemotherapy, while uncommon, can lead to tissue necrosis and require reconstructive surgical repair. It can be difficult to verify if a drug extravasation has occurred because symptoms vary and may be delayed. Usually, extravasation is identified by immediate swelling, pain, and/or redness at the site of infiltration. Subsequent further swelling and blistering may occur, followed later by ulceration and tissue necrosis. Many local measures such as ice packs, injection of steroids or bicarbonate solutions, topical steroids, and dimethylsulfoxide have been tried to prevent tissue damage without clear evidence of success. Estimating the amount of anthracycline reaching perivenous tissues and the likelihood of serious tissue damage is difficult. Therapy other than surgery has been of uncertain benefit; the timing, frequency, and indications for surgical resection and repair of damaged tissue are not well defined.

The frequency of extravasation and the frequency of subsequent required surgical interventions are uncertain. A retrospective report from the University of Texas MD Anderson Cancer Center in 2002 described an incidence of extravasation of 0.01% of chemotherapy infusions over a 6-year interval [1]. Among 44 extravasation cases followed in a 2-year interval, 15 were ascribed to paclitaxel and 12 to doxorubicin. Only 26 of the 44 patients were referred to a surgeon. Of these 26, 10 patients had surgery performed for extravasation-related tissue injury. The majority of the surgeries resulted from cases involving doxorubicin administration (personal communication from the author, H. Langstein). Satisfactory wound healing without surgery occurred in all the others.

In the U.S., anthracyclines are typically administered i.v. through a central venous access device (CVAD) such as an implantable port or central venous catheter. Before these options were commonly available, anthracyclines had been given via a temporary i.v. needle placed for the purpose of giving that day’s treatment. After i.v. access, anthracycline chemotherapy is typically administered as a short i.v. infusion along with a fluid solution to provide rapid dispersal, dilution, and circulation of the drug.

In 1993, Danish investigators reported a management strategy for extravasation [2]. Extravasation was suspected based on symptoms of swelling, redness, and/or pain at the administration site, usually a peripheral i.v. location. Small tissue biopsies of the infiltration area were performed and examined for tissue fluorescence microscopically under UV light. Because anthracyclines exhibit fluorescence under these conditions, this procedure can indicate the presence of anthracycline in perivenous tissue, confirming that extravasation has occurred. Among 22 patients suspected of having an anthracycline extravasation, nine patients whose biopsies were negative for fluorescence were observed without intervention and none showed sequelae. Thirteen patients with fluorescence-positive biopsies had prompt surgery intended to remove the damaged tissue area and residual tissue anthracycline. Despite surgery, eight of 13 had sequelae such as skin ulceration, atrophy, or limitation of motion. In addition to its limited benefits, surgery may also cause a delay in subsequent chemotherapy treatment cycles until adequate wound healing has occurred. Based on that experience and prior to the conduct of efficacy studies, the applicant advised the FDA that the standard of care in Denmark was to perform tissue biopsies upon suspected extravasation, to examine the biopsies for tissue fluorescence, and to proceed with surgery for those patients with fluorescence-positive biopsies.

CLINICAL STUDIES
The applicant conducted two multicenter clinical studies, the first in Denmark and the second in Denmark and additional European sites, testing the effect of dexrazoxane given after extravasation on reducing the need for surgical intervention for tissue injury. Because the stan-
standard of care in Denmark was to resect extravasations found to be fluorescence-positive, the sponsor and the investigators considered an observation-only control arm as unethical as well as not feasible because of the rarity of the extravasation event. Each study consisted of a single-arm, open-label enrollment of sequential eligible patients. The major eligibility criteria for patients in both studies were: (a) receiving an i.v. anthracycline alone at the time of the extravasation (patients could have received other agents sequentially prior to the anthracycline); (b) suspected anthracycline extravasation, based on at least one of the following: immediate symptoms of pain, swelling, and/or redness while receiving the drug via a peripheral i.v. or CVAD; and (c) no use of dexrazoxane prior to chemotherapy.

For patients to be considered evaluable for efficacy, prospectively defined conditions were: (a) the performance of skin biopsies, (b) fluorescence confirmed in the tissue sample, and (c) initiation of dexrazoxane therapy within 6 hours of the event.

Patients could receive initial therapy with dexrazoxane prior to determination of the skin fluorescence results. If biopsy fluorescence was not detected, patients were not given additional dexrazoxane and were not assessed for efficacy but were assessed for safety. Also, to be evaluable for efficacy, patients had to begin dexrazoxane as soon as possible and no more than 6 hours following the event. (The 6-hour interval was derived from nonclinical studies described briefly below.) The dexrazoxane treatment was given by i.v. infusion over 1–2 hours for three consecutive days: 1,000 mg/m² on the day of the event, 1,000 mg/m² 24 hours later, and 500 mg/m² on the third day, given through an i.v. access site different from the extravasation site. Doses were capped at 2,000 mg on days 1 and 2 and at 1,000 mg on day 3. This 3-day schedule was the complete treatment course. Patients were followed for up to 90 days. Those showing signs of worsening skin reaction, defined as blistering or necrosis, were to have resection performed for blistering or necrosis according to the local surgeon’s judgment. Color photographs of the extravasation site were performed serially on each patient and submitted for FDA review.

**Efficacy Results**

Because the eligibility and management plans were identical and the enrolled patient populations very similar, the results of the two studies were pooled for analysis. In total, 80 patients were enrolled and 57 were considered evaluable on the basis of photography, positive biopsy fluorescence (in 54 of 57), and receipt of the first dexrazoxane infusion within 6 hours of the event. The three patients without biopsies had clinically diagnosed extravasations involving CVADs. Epirubicin was the anthracycline involved in 56% of cases and doxorubicin was involved in 41% of cases. Two patients received daunorubicin. No patients were receiving other i.v. chemotherapy simultaneously. Peripheral i.v. sites of extravasation included the forearm in 63%, the hand in 21%, and the antecubital area in 11%; four patients (5%) received the anthracycline via a CVAD. Most patients presented with swelling (83%), redness (78%), and pain (43%). Blistering occurred in 11%. The median baseline lesion area was 25 cm² (range, 1–253 cm²). Timing of the onset of extravasation symptoms varied from early to late during the anthracycline infusion procedure. Estimates of the quantity of anthracycline infused prior to recognition varied from 10% of the drug infused to 90% of the infusion for one of the CVAD patients. Amounts of anthracycline in tissue could not be estimated.

In study 1, none of the 19 evaluable patients required surgical intervention and none had serious late sequelae.

In study 2, one of the 38 evaluable patients required surgery for nonresolving tissue injury. Thirteen patients had late sequelae at the event site such as site pain, fibrosis, atrophy, and local sensory disturbance; all were judged as mild except in the one patient who required surgery. None of the four patients with CVADs required surgical intervention. One additional patient of the 80 enrolled, who required surgery for tissue necrosis, was considered nonevaluable because of the concomitant use of several nonprotocol therapies including applications of local cooling of the site with ice before and during the dexrazoxane infusions.

**Adverse Reactions**

In the two studies, the adverse reaction profile described in the labeling reflects the combination of dexrazoxane, the underlying disease, and the chemotherapy. Dexrazoxane is a cytotoxic drug.

Some information on the safety of i.v. dexrazoxane administered alone, as well as in combination with anthracyclines and other chemotherapies, is available in literature reports. In a phase II study of dexrazoxane for the treatment of AIDS-related Kaposi’s sarcoma, 13 patients received 1,000 mg/m² per day for 3 days every 3 weeks, with dosage adjustment based on nadir granulocyte and platelet counts. Treatment-emergent neutropenia and thrombocytopenia necessitated dosage reduction in several patients [3]. In a study of single-agent dexrazoxane in the treatment of non-small cell lung cancer, i.v. doses of 1,500 mg/m² daily were administered for three con-
secutive days, repeated every 3 weeks. Neutropenia was dose limiting [4]. In addition to bone marrow suppression, temporary infusion site pain, nausea, vomiting, diarrhea, stomatitis, and transient alterations in liver function have been observed.

**NONCLINICAL SUPPORTIVE STUDIES**

In a series of nonclinical studies, the applicant demonstrated that dexrazoxane administration soon after a s.c. injection of doxorubicin, daunorubicin, or idarubicin reduces or prevents the formation of cutaneous lesions in mice [5, 6]. In these experiments, investigators injected a single dose of an anthracycline such as doxorubicin or daunorubicin under the skin of a mouse. A wound usually developed in the overlying skin and in the underlying tissue over the course of 4–5 days. The wounds formed an eschar and healed over the course of 20–40 days depending on the size and severity. The investigators quantified the effect of dexrazoxane on wound area (using bidimensional measurements) and then plotted time versus wound area to obtain an area under the curve. They also quantified the effect of dexrazoxane by comparing the number of mice that developed a wound after receiving dexrazoxane with untreated controls. Figure 2 demonstrates how dexrazoxane decreased the severity of cutaneous wounds in a typical nonclinical experiment with doxorubicin. In other experiments (not shown) dexrazoxane decreased the time necessary for wound healing.

The sample sizes in these nonclinical experiments were small (usually \( n = 7–9 \) per dose group), limiting the power of the statistical analysis. The FDA performed a logistic regression analysis of data pooled across multiple but very similar experiments in mice given a dose of daunorubicin s.c. and found that the incidence of wound formation decreased with increasing dexrazoxane dose. The 50% effective dose for the prevention of wound formation was about 200 mg/kg (600 mg/m²). Figure 3 depicts this analysis. The \( p \)-value for the regression was < .0001 (\( \chi^2 \)), supporting a significant relationship. An analysis of the combined doxorubicin data gave similar results (not shown).

Dexrazoxane has also shown some beneficial effect against epirubicin and mitoxantrone in the nonclinical setting. The sponsor’s battery of studies suggested that dexrazoxane probably does not mitigate damage by scavenging radicals at the damage site or by chelating iron ions. The dexrazoxane effect may be related to its binding to a site on DNA close to but distinct from the binding site of anthracyclines, thereby preventing the binding of the anthracycline and the resultant double-strand breaks associated with the inhibition of topoisomerase II [7–10]. Experimental results in mice demonstrated that dexrazoxane given immediately after anthracycline extravasation is significantly more effective than delayed treatment. Efficacy in mice diminished rapidly 6 hours after the anthracycline toxic insult.

In short-term toxicity nonclinical studies, a total dose of dexrazoxane of up to 600 mg/kg (3,600 mg/m²) given as two doses in a 24-hour period caused minimal toxicity in rats. In 28-day toxicology studies in rats, dexrazoxane at doses as high as 200 mg/kg (1,200 mg/m²) caused no mortality but did cause weight loss, myelosuppression, and anemia. Repeat dosing caused microscopic damage in the spleen, thymus, lymph nodes, and testes and there was some evidence of renal and hepatic injury.

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**Figure 2.** Time versus wound area following anthracycline with or without dexrazoxane. In this experiment, a single dose of 250 mg/kg dexrazoxane given i.p. immediately after a dose of 3 mg/kg daunorubicin s.c. decreased the mean wound area under the curve from 1,050 mm²/day in controls \( (n = 7) \) to 433 mm²/day \( (n = 6) \).
DISCUSSION

Dexrazoxane received FDA approval in 1995 for reducing the incidence and severity of cardiomyopathy associated with doxorubicin administration in women with metastatic breast cancer who have received a cumulative doxorubicin dose of 300 mg/m² and who continue to receive doxorubicin therapy. For this use, dexrazoxane is given immediately before doxorubicin i.v. in a ratio (in milligrams) of 10:1 dexrazoxane:doxorubicin. In Europe, a 20:1 ratio is used. Thus, in Europe, a typical schedule for cardioprotection in a patient receiving 50 mg/m² of doxorubicin includes a single dose of 1,000 mg/m² of dexrazoxane given immediately prior to doxorubicin. From this experience, the sponsor selected the 3-day schedule used in the clinical studies. Renal excretion of dexrazoxane is substantial; based on a model of systemic exposure, the dose should be reduced by 50% in patients with creatinine clearance values <40 ml/minute. The possible benefit of alternative dose schedules has not been examined. The sponsor is conducting a population pharmacokinetic analysis to compare population parameter estimates and interindividual variability with literature values for dexrazoxane. There are no known drug interactions.

Extravasation is an uncommon but important complication of anthracycline therapy for which randomized studies are not practical and management has not been well defined. Partly because of this concern, contemporary usual practice in the U.S. has evolved to administer anthracyclines by CVADs. Upon FDA review, the extravasations studied were considered representative of the anthracycline extravasation experience for both peripheral i.v. and CVAD use. The outcomes were favorable, with minimal sequelae and only one of 57 evaluable patients requiring surgical intervention. The study patients had evidence of anthracycline in tissue, although this test is not considered necessary for clinical care. While the true frequency of surgical intervention is uncertain in this population, it is probable that 10%–25% of the patients, most of whom had peripheral site extravasations, would have required surgery in the absence of dexrazoxane treatment to avoid chronic necrosis or other morbidity. In conjunction with the supportive controlled nonclinical studies performed by the sponsor, the FDA
concluded that the demonstrated benefit of dexrazoxane sufficiently outweighed its risk and granted regular approval for this indication.

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REFERENCES


AUTHOR CONTRIBUTIONS
Collection/assembly of data: Robert C. Kane, W. David McGuinn, Jr., Ramzi Dagher
Data analysis and interpretation: Robert C. Kane, W. David McGuinn, Jr.
Manuscript writing: Robert C. Kane, W. David McGuinn, Jr., Ramzi Dagher
Final approval of manuscript: Robert Justice, Richard Pazdur