

# A Focus on the Treatment of Anthracycline Extravasation and Tissue Protection

Seppo W Langer, MD, PhD,<sup>1</sup> Maxwell Sehested, MD, PhD<sup>2</sup> and Peter Buhl Jensen, MD, PhD<sup>1</sup>

1. Consultant Medical Oncologist, Department of Oncology; 2. Consultant Pathologist, Copenhagen University Hospital

### Abstract

Accidental extravasation of anthracycline-based chemotherapy is a complication that has been feared since the introduction of the anthracyclines more than 40 years ago. Tissue infiltration with vesicant drugs may lead to progressive necrosis and destruction of muscles, tendons, nerves, and joints, and may be associated with severe functional and cosmetic changes. During the last four decades, much effort has been made to prevent such accidents from happening. In addition, different surgical approaches and several non-pharmacological and pharmacological treatments have been used to counteract the devastating effects of the extravasation. Most treatment modalities have been empirically based, and only a few have undergone thorough evaluation. Recently, dexrazoxane was shown to be an effective and non-toxic acute treatment for anthracycline extravasation. It has since become a widely recommended treatment, and Totect® is currently the only approved drug for this indication.

### Keywords

Anthracycline, extravasation, dexrazoxane, tissue protection, doxorubicin, Totect

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**Correspondence:** Seppo W Langer, MD, PhD, Department of Oncology, Section 5073, Copenhagen University Hospital, Rigshospitalet, DK-2100 Copenhagen, Denmark.  
E: seppo.langer@rh.regionh.dk

## Anthracycline Extravasation

For 40 years, the use of anthracycline anticancer drugs has been a mainstay in the curative and palliative treatment of many solid tumors and hematological malignancies. Millions of patients have received treatment with doxorubicin, epirubicin, daunorubicin, and several newer analogs. Regrettably, a small fraction of patients have suffered from the unintentional extravasation of these drugs, which is a potentially devastating complication.

After the unintended leakage into the peri-vascular tissues, the clinical course is characterized by redness and swelling. Pain may be present, but is not mandatory for diagnosis. Within days to weeks, blisters, ulceration, and necrosis may occur, and the tissue destruction may continue into adjacent areas. Anthracyclines have a propensity to persist in tissues for months.<sup>1,2</sup> Accordingly, the progressive tissue destruction may continue for weeks and even months.

The tendency to form necrosis and ulceration depends in part on the amount and concentration of the anthracycline. Other factors that may play a role are host factors such as the location and venous flow. Not all anthracycline extravasations develop into ulceration. However, for significant extravasations the risk is estimated to be 25–50%.<sup>3–8</sup> Unless treated, the complication may cause short-term defects, infections, and discontinuation of the

scheduled antineoplastic treatment, as well as long-term cosmetic and functional defects.<sup>7,9,10</sup>

## Prevention

Following the initial descriptions in the 1970s of progressive ulceration and destruction of deeper neurovascular or tendon structures, it became clear that every precaution should be taken to prevent extravasations.<sup>11,12</sup> Intense surveillance by the treating nurse during anthracycline infusion has since then been routinely carried out in most oncology institutions.<sup>13</sup> Other preventive measures include the use of central venous access devices that may reduce the risk for extravasation; however, this does not completely eliminate the risk.

## Surgical Treatment

There are no uniform guidelines for the surgical treatment of anthracycline extravasations. It has generally been agreed that for significant extravasations, surgery should be performed to remove the tissue-bound anthracycline. Often, only the timing of the intervention has been open for discussion, i.e. early versus late surgery.<sup>3,4,9,12,14</sup> During surgical excision, wide margins encompassing all anthracycline-containing tissues are often adopted. The procedure may be guided by fluorescence microscopy of margins, and may necessitate skin grafting.<sup>4,5,9,15,16</sup> The presence of blisters or severe pain

has also been indicative for surgical intervention. For small or intermediate-sized extravasations, there has been a problem establishing the diagnosis, and controversy has therefore existed around the use of surgical intervention.

Saline-flushing of the infiltrated tissue through multiple incisions is a surgical technique that has been adopted by some institutions.<sup>17,18</sup> However, it is time-consuming, and will not remove all of the extravasated anthracycline. No biopsy-verified studies have been conducted to demonstrate its efficacy.

In our experience, the incidence of surgical anthracycline treatment diminishes dramatically with the introduction of dexrazoxane

associated with somewhat reduced efficacy.<sup>37</sup> Finally, it was shown that topical DMSO actually had a tendency to decrease the efficacy of dexrazoxane.

### Clinical Experience with Dexrazoxane

The experimental results were soon translated into pilot clinical use. First, we briefly described the successful dexrazoxane treatment of two patients with large anthracycline extravasations; one patient had a biopsy-proven epirubicin extravasation of her forearm, while the other had a large chest wall doxorubicin extravasation from a central catheter.<sup>38</sup> No surgical intervention became necessary, and no sequelae were observed. Several subsequent case reports confirmed the feasibility of the treatment.<sup>39-41</sup>

In 2007, the results of the two prospective European multicenter trials, TT01 and TT02, were presented.<sup>42</sup> A total of 80 patients were included from 17 and 24 European oncology and hematology centers, respectively. The studies were very similar, and consequently was the data compiled. In both studies, extravasations had to be confirmed by fluorescence-positive biopsies; this was the case in 57 evaluable patients. The anthracyclines most commonly involved were epirubicin (56%) and doxorubicin (41%). The affected skin areas in confirmed anthracycline extravasations were of a median of 24cm<sup>2</sup> and 39cm<sup>2</sup> in the two studies, respectively.

The first dose of dexrazoxane was given as soon as possible and within six hours of extravasation as a one- to two-hour intravenous (IV) infusion through a different venous access location than the extravasation site. After the first dose, treatment was repeated 24 and 48 hours later for a total of three doses. The first and second doses were 1,000mg/m<sup>2</sup> and the third dose was 500mg/m<sup>2</sup>, up to a maximum daily dose of 2,000mg on days one and two and 1,000mg on day three.

After dexrazoxane treatment, only one of the 57 evaluable patients required surgery. This patient had suffered from a massive extravasation involving most of her forearm and hand. Dexrazoxane

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(Savene® in Europe and Totect® in the US). We outline evidence from experimental studies and clinical use in the paragraphs below.

### Non-surgical Treatment

The list of non-surgical, mostly local, treatment modalities that have been used experimentally against anthracycline extravasation injuries is very long. Some of the most clinically used managements are cooling,<sup>4,9,19,20</sup> topical dimethyl sulfoxide (DMSO),<sup>21-28</sup> topical and intralesional hyaluronidase,<sup>29</sup> or corticosteroids.<sup>3,30-32</sup> The rationale for using these treatments ranges from free radical scavenging, changing of skin permeability, and enhanced anthracycline absorption to anti-inflammatory treatment, but from both a clinical and pre-clinical perspective, the documentation is poor.

### Experimental Studies with Dexrazoxane

A turning point in the treatment of anthracycline extravasation emerged with the discovery that the bisdioxopiperazine dexrazoxane had a hitherto unseen high efficacy in preventing experimentally induced anthracycline ulcers. The background for these experiments was the recognition that dexrazoxane is a catalytic inhibitor of DNA topoisomerase II and, additionally, acts as a strong metal ion chelator that is able to remove iron from the iron-anthracycline complex, as well as preventing the formation of reactive oxygen species.<sup>33,34</sup> The exact mechanism of action in which dexrazoxane acts as an antidote in tissue extravasation injuries has not yet been identified.

In a large number of animal experiments, not only was it possible to demonstrate a highly significant reduction in both frequency and size of ulcers, but also complete prevention of anthracycline-induced ulcers was achieved with repeated doses of systemic dexrazoxane.<sup>35,36</sup> It was noted that delayed treatment was also

*A recent review of clinical cases with anthracycline extravasation from central venous access devices also confirms the marked efficacy of systemic antidotal treatment with dexrazoxane.*

was shown to enable the continuation of planned chemotherapy with minimal delay in the majority of patients with limited hospitalization due to the extravasation. The most commonly seen side effects were mild pain at the infusion site and reversible increases in liver enzymes. Thirteen patients had late sequelae at the event site such as pain, fibrosis, atrophy, and local sensory disturbance; however, all were mild (common toxicity grade 1) except in the patient who required surgery. The treatment was well tolerated.

Finally, among the 27 remaining dexrazoxane-treated extravasations in study TT01 and TT02 in which anthracycline extravasation was suspected but not verified by biopsies, none progressed into ulceration.

A recent review of clinical cases with anthracycline extravasation from central venous access devices also confirms the marked efficacy of systemic antidotal treatment with dexrazoxane.<sup>43</sup>

In September 2007, dexrazoxane was approved in the US by the US Food and Drug Administration (FDA) under the brand name Totect for the treatment of anthracycline extravasation, and the code 999.81 has recently been added to the 2009 ICD-9-CM code system to describe extravasation of vesicant chemotherapy.<sup>44</sup>

## Summary

For 40 years of treatment with anthracycline-based chemotherapy, extravasation has been a feared complication. Dexrazoxane represents the first documented and licensed antidote against anthracycline extravasation injuries. It is associated with a positive risk-benefit ratio and may prevent considerable morbidity in patients undergoing anthracycline-based chemotherapy for cancer. ■



Seppo W Langer, MD, PhD, is a Consultant Medical Oncologist in the Department of Oncology at Copenhagen University Hospital. He is a board-certified specialist in internal medicine and medical oncology and holds a PhD in pre-clinical studies of anthracycline extravasation.



Maxwell Sehested, MD, PhD, is Chief Scientific Officer at TopoTarget and a Consultant Pathologist at Copenhagen University Hospital. He is a board-certified pathologist with a PhD in pre-clinical cancer therapeutics in the field of multidrug resistance.



Peter Buhl Jensen, MD, PhD, is Chief Executive Officer of TopoTarget. He is an Honorary Professor of Oncology at the University of Copenhagen and a Consultant Medical Oncologist at Copenhagen University Hospital. He is a board-certified specialist in internal medicine and medical oncology and holds a PhD in pre-clinical cancer therapeutics evaluation.

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