

## Managing Anthracycline Extravasations and Protecting Tissue

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### Abstract

Accidental leakage of a chemotherapy drug from the vein into the surrounding tissue can lead to severe and permanent disability. The degree of injury associated with an extravasation can range from a very mild skin reaction to severe necrosis, the severity of which relates to whether a drug binds to the DNA of the cell or not. The management of extravasations remains largely based on anecdotes of effective interventions that are based mostly on case studies, and healthcare professionals face the challenge of determining best practice based on a meagre body of evidence. However, recent advances in extravasation treatment are improving patient outcomes: the incidence of tissue necrosis can now be significantly reduced and, in some cases, prevented.

### Keywords

Anthracycline extravasations, tissue protection, evidence-based guidelines

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Chemotherapeutic agents are associated with various adverse events and, with over one million intravenous (IV) chemotherapy infusions and injections given worldwide every day, the main patient safety focus for healthcare professionals is to minimise events and complications for patients. However, in a relatively small number of cases, accidental leakage of the chemotherapy drug from the vein into the surrounding tissue can lead to severe and permanent disability.<sup>1</sup> The degree of injury associated with an extravasation can range from a very mild skin reaction to severe necrosis, the severity of which relates to whether a drug binds to the DNA or not.<sup>2</sup>

In cancer care, an extravasation is defined as “the non-intentional leakage of substances into the perivascular or subcutaneous space that can result in significant tissue damage”.<sup>3</sup> The incidence of extravasations is 0.5–6%, and the incidence of this type of injury if tissue damage occurs has been noted to be as high as 22% in adults.<sup>4</sup> Data regarding extravasation from central lines are more limited. One small study estimated that extravasation occurs about 6% of the time;<sup>5</sup> however, it is thought that many of these events are not reported, and the true frequency is therefore not known. Some extravasations can be accounted for by error due to the nurse’s and/or physician’s lack of skill in the IV procedure; however, many cases are due to high-risk patients, since patients receiving these cancer therapies have multiple risk factors that make IV infusion complicated.<sup>6</sup>

It is unknown whether all vesicant extravasations result in the same sequence of injury; however, the common theory for doxorubicin extravasations is that when the affected cells die, the drug is released and absorbed by healthy cells, which over time leads to

progressive damage.<sup>7</sup> Cells and cell membranes are also damaged by superoxide, hydroxyl and peroxide radicals that are generated by the anthracyclines in paravenous tissues, causing damage to small blood vessels and thus leading to a loss of vascular integrity.<sup>8</sup> These degenerative changes continue for weeks and impair normal healing.

Although uncommon, this adverse event has the potential to affect patient quality of life and survival and generate substantial healthcare costs. Our knowledge of the management of extravasations remains largely based on effective interventions, mostly based on case studies describing possible interventions, and thus is also highly individualised. Based on this knowledge, healthcare professionals face the challenge of determining best practice based on a meagre body of evidence. However, lately advances in the treatment of extravasations are improving patient outcomes in terms of the incidence of tissue necrosis, and the need for operation can now be significantly reduced and, in most cases, prevented.<sup>9,10</sup>

### DNA-binding Agents

Chemotherapy is commonly grouped into three broad categories based on propensity to cause tissue damage upon extravasation: non-vesicants, irritants and vesicants. Non-vesicants do not cause ulceration. If extravasated, they rarely produce an acute reaction or progress to necrosis. Irritants tend to cause pain at and around the injection site and along the vein. They may also cause inflammation. Some irritants have the potential to cause ulceration, but only in cases where a very large amount of the drug is extravasated into the tissue.<sup>6</sup> Vesicants have the potential to cause blistering and ulceration if left untreated, and can lead to the more serious side effects of extravasation, such as tissue destruction and

necrosis. These drugs are sub-classified according to the way in which they cause damage; this is important, since it affects the management strategy.

DNA-binding agents can be divided into three categories: anthracyclines (doxorubicin, daunorubicin, mitoxantrone and idarubicin), antitumour antibiotics (mitomycin) and some alkylating agents.<sup>11</sup> Anthracyclines bind to nucleic acids in DNA and lead to multiple breaks in DNA strands by being toxic to topoisomerase II. They generate free radicals, which inhibit RNA and protein synthesis and, ultimately, cause cell death. Free radicals are unstable molecules since they have lost electrons and, as such, are very reactive to missing electrons from other molecules.<sup>11,12</sup>

**Risk Factors**

Patients with cancer are at increased risk of soft-tissue injury due to their debilitated state from the illness, as well as any previous IV treatment.<sup>13</sup> To aid in the prevention of extravasations, certain risk factors should be taken into account before administration of these agents. Risk factors for extravasations can be patient-, equipment-, location-, agent- or clinician-related (see Table 1).

**Initial Symptoms**

Extravasations must be distinguished from other reactions, such as flare reaction or recall phenomenon. Confirming an extravasation during drug administration can be a challenge, since manifestations vary. The initial symptoms of extravasation can include: discomfort and/or pain, which can range from mild to intense, and is often described as a burning sensation; obvious swelling; erythema; and loss of blood return. These symptoms can also appear hours or even days later.<sup>14</sup> The initial symptoms of extravasation can be subtle and similar for the extravasation of different agents, but the progression of these initial symptoms differs greatly for irritants and vesicants, particularly relating to permanent damage to the tissue.<sup>6</sup> It is of great importance that proper procedures are in place to follow up and monitor how the anthracycline treatment is working.

Most extravasation protocols call for the immediate cessation of delivery, followed by extensive measures to prevent further spread of the cancer therapy into the tissue. As a result, the delivery of

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chemotherapy treatment may be delayed until the extravasation is resolved. Some guidelines specifically address the matter of re-establishment of chemotherapy treatment, recommending the establishment of an intravenous access in the other limb. However, most guidelines do not specifically address this process.<sup>6</sup>

**Tissue Damage**

Vesicants such as anthracyclines have the potential to cause extensive tissue damage upon extravasation from the bloodstream.

**Table 1: Risk Factors for Extravasations**

Risk Factor	Example
<b>Patient-related</b>	
	Age (very young or old)
	Impaired communication
	Compromised circulation
	Altered sensory perception
	Poor understanding of risk (anxiety, fear, cultural concerns, medication)
<b>Equipment-related</b>	
	Large-gauge catheters, metal needles
<b>IV access-related</b>	
Central venous access	IV post-separation or dislodgement, fibrin development
Peripheral access	Inadequately secured needle, inappropriate size of needle Poorly secured needle or catheter, undesirable choice of IV location
<b>Agent-related</b>	
	Vesicant, volume infiltrated, drug concentration, repeated use of vein
<b>Clinician-related</b>	
	Lack of IV skills and knowledge
	Interruptions/distractions during IV administration

*IV = intravenous. Based on information from European Oncology Nursing Society (EONS) extravasation guidelines, 2007.<sup>14</sup>*

The most commonly seen extravasations are those involving anthracycline, such as epirubicin. Tissue destruction caused by leakage of vesicants into surrounding tissue is progressive in nature and symptoms may progress slowly with minor pain; however, anthracycline extravasations are characterised by severe pain and swelling depending on the amount of drug that has been extravasated.<sup>13</sup> Indurations or ulcer formation are by no means immediate phenomena – they develop over weeks and months and are extremely slow to heal. In general, tissue damage begins with the appearance of inflammation and blisters at or near the site of administration. The chronic progression of the tissue damage is due to the fact that the drug cannot be locally metabolised or removed from the area by lymphatic circulation, and may also be enhanced by the effects of prior radiotherapy or doxorubicin treatment.<sup>13</sup>

The tissue damage can progress to ulceration, in some cases progressing all the way to necrosis of the local tissue. Necrosis can occasionally be so severe that function in the affected area cannot be recovered and surgery is required. Damage from an extravasation can occur in skin and subcutaneous tissue and, if the extravasation should occur next to a nerve, ligament or tendon, the damage may extend to that tissue and may affect both sensation and function. Manifestations of central venous catheter extravasations may be less obvious; since there are variations depending on the location and the size of the areas involved, extravasations from central catheters potentially involve larger areas as symptoms may debut at a later time-point due to the fact that the extravasation occurs deep down in the tissue that may be extravasated.<sup>14</sup> Mediastinal and chest extravasations may cause chest or substernal pain, burning sensations, palpitations, fever, cough or dyspnoea.<sup>15-17</sup> The potential for tissue damage is also influenced by drug concentration and the amount of drug infiltrated, the duration of tissue exposure and the site of the leakage. As such, large-volume extravasations of highly

concentrated DNA-binding vesicants are very difficult to manage. The timing of extravasation interventions is important, since any delays in recognition may well mean increased injury, pain and disability.<sup>11</sup>

## Initial Management

Optimal management of extravasation demands ongoing collaboration and communication among the multidisciplinary team. The use of conservative measures, such as applying cold or heat and elevating the affected extremity, have been used for many years; however, the evidence of the benefit for this is mainly empirical. The same is true for any withdrawal of extravasated vesicants. Applying cold compresses is proposed for anthracycline extravasations, since cold causes vasoconstriction, which, in turn, may decrease local dispensation and slow down cellular uptake of drug, and is thus thought to reduce the extent of injury.<sup>18</sup>

## Pharmacological Management

Savene® (dexrazoxane) is approved and used for the treatment of extravasations as a result of anthracycline treatment.<sup>19</sup> With 98% efficacy, this new treatment has revolutionised the way in which extravasations are treated today. Savene has two major mechanisms of action: chelation of iron, reducing iron-dependent free radical oxidative stress associated with anthracycline toxicity, and inhibition of DNA topoisomerase II. While both mechanisms may contribute to the overall protective effects of Savene in anthracycline extravasation, it must be noted that the extent to which either iron chelation or inhibition of DNA topoisomerase II contributes to these effects is unknown.

Savene is supplied as a single-use treatment kit, and is a systemic treatment that is infused over one to two hours daily for three days using a large vein in an area away from the extravasation site. Administration of Savene should begin as soon as possible and no later than six hours after the extravasation. The dosing is based on the patient's body surface area, with a dose of 1,000mg/m<sup>2</sup> given on the first two days and a dose of 500mg/m<sup>2</sup> given on the third day. For those patients with a body surface area  $\geq 2\text{m}^2$ , a maximum dose of 2,000mg on the first two days and 1,000mg on the third day is advised. For patients with creatinine clearance values  $< 40\text{ml/minute}$ , the dose should be reduced by 50%. If topical cooling is used, it should be removed at least 15 minutes prior to and during the treatment and should not be applied again until four to six hours after stopping the Savene treatment. The patient needs close

monitoring for any side effects, such as nausea and vomiting, diarrhoea, stomatitis, infusion-site burning, elevated liver enzyme levels and bone marrow suppression.<sup>19,19</sup> It is crucial that patients are educated about the possible side effects of anthracycline administration in order to react promptly if symptoms occur.

Progressive extravasation injuries in progress are painful, and non-opioids may be beneficial; however, there may be a need to use opioids for adequate pain control, especially if the pain interferes with movement, daily activities and/or rehabilitative efforts.<sup>13</sup>

## Non-pharmacological Management

Surgery is not the initial treatment option for extravasations, but is warranted when pain, inflammation or ulceration of tissue continues despite local treatment measures. However, older evidence has previously supported immediate surgery as the method of choice for anthracycline extravasations, since these agents tend to bind to fat and produce soft-tissue necrosis.<sup>20</sup>

## Conclusion

The most important approach to minimising the consequences of extravasation is prevention. There is a tendency to take the conservative approach, that 'this is the way we have always done it', and in this scenario older local guidelines have to change to align with the newly developed extravasation guidelines, in which Savene represents the first documented and licensed antidote against anthracycline extravasation injuries. Healthcare professionals involved in the handling and administration of intravenous cancer treatment should become familiar with local procedures and protocols and develop an understanding of the important precautionary steps that should be taken to minimise extravasation and the resulting injuries. ■



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