

# Systematic review on the efficacy of dexrazoxane in managing extravasation of anthracyclines

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## ABSTRACT

**Introduction** Extravasation of anthracyclines is an uncommon but serious complication of systemic anticancer therapy (SACT), potentially causing significant tissue injury, treatment delays and psychological distress. Dexrazoxane is the only licensed pharmacological antidote for anthracycline extravasation; however, its real-world use, dosing adherence and clinical outcomes remain poorly characterised. This systematic review evaluates the clinical efficacy of dexrazoxane, assesses variations in its administration, summarises additional management strategies and describes reported patient outcomes.

**Research design and methods** A systematic search was conducted in MEDLINE, EMBASE and CINAHL for studies published between January 2000 and June 2024. The review protocol was registered with PROSPERO (CRD42024611046). Data extraction captured patient demographics, dexrazoxane use, dosing adherence, surgical interventions, adjunct therapies and outcomes. Risk of bias was assessed using the Joanna-Briggs Institute checklist for case reports. Reporting followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

**Results** Sixteen articles describing 21 individual extravasation cases were included, all were categorised as low risk of bias. Dexrazoxane was administered in all cases; but licensed dosing was followed in only 52% (n=11). Variations included modified schedules, delayed administration and use of unlicensed products. Six patients (29%) required surgery in addition to pharmacological management. No limb loss occurred, and all patients recovered, with recovery ranging from days to months. Seven (33%) resumed SACT post-recovery. The range of adjunctive measures reported across the studies, reflected the absence of standardised extravasation management.

**Conclusion** Significant variation exists in dexrazoxane use and dosing when managing anthracycline extravasation. Given the limited case numbers and heterogeneity, definitive conclusions regarding the efficacy of dexrazoxane cannot be drawn.

**PROSPERO registration number** CRD42024611046

## INTRODUCTION

Extravasation, the inadvertent administration of a drug into the surrounding tissue rather than the intended vein, represents a significant complication of systemic anticancer therapy (SACT). Reported incidence rates

## WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Anthracycline extravasation is a rare but significant complication of systemic anticancer therapy, with dexrazoxane licensed as the only licensed antidote, yet evidence on consistent dosing and real-world practice remains limited.

## WHAT THIS STUDY ADDS

⇒ This review demonstrates that dexrazoxane is frequently used for anthracycline extravasation but is often administered with variations from the licensed protocol.

## HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ These findings highlight the need for clear, standardised protocols, education of healthcare professionals around using the standardised protocols and systematic data collection to inform guidelines and improve patient outcomes in extravasation management.

of SACT-related extravasation vary widely, ranging from 0.1% to 6%.<sup>1,2</sup> The resulting tissue damage not only causes physical harm but also contributes to considerable psychological distress for patients.<sup>3</sup> Moreover, recovery from extravasation injuries may necessitate delays in SACT administration, potentially compromising treatment outcomes.<sup>4</sup> To minimise these adverse effects, early recognition and immediate intervention are essential. Accordingly, all healthcare institutions delivering SACT should implement standardised guidelines for the prevention and management of extravasation.<sup>1</sup> In more severe cases, particularly those involving necrosis, surgical intervention may be required to remove damaged tissue and prevent further complications. The extent of tissue injury is influenced by several factors, including the pharmacologic profile of the extravasated agent and patient-specific variables such as vascular integrity and comorbid



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conditions.<sup>5,6</sup> Additionally, the prospect of litigation and financial compensation may arise, further underscoring the clinical and legal significance of this issue.<sup>7</sup>

In the UK, voluntary reports of extravasation incidents between 2010 and 2012 identified anthracyclines as one of the most frequently implicated agents in extravasation-related injuries.<sup>8</sup> Dexrazoxane, a parenterally administered antidote, is specifically used to manage anthracycline extravasation. It was licensed in Europe under the trade name *Savene* in 2006, and subsequently in the USA as *Totect* in 2007.<sup>3,9–12</sup> Although the precise mechanisms by which dexrazoxane mitigates tissue damage remain unclear,<sup>2,13,14</sup> its clinical benefit lies in its ability to significantly reduce the size and duration of wounds, resulting from anthracycline extravasation as well as the need for surgical intervention.<sup>14</sup> Other brands of dexrazoxane include *Zinecard* approved by the U.S. Food and Drug Administration (FDA) in 1995 and discontinued in 2020 and *Cardioxane* approved by Europe in 2006, these are licensed as a cardioprotective agent caused by anthracycline use. Generic dexrazoxane is also available in some countries.

#### Licensed indications:

**Savene**—indicated in adults for the treatment of anthracycline extravasation.<sup>10</sup>

**Totect**—treatment of extravasation resulting from intravenous anthracycline chemotherapy/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/m<sup>2</sup> and who will continue to receive doxorubicin therapy to maintain tumour control.<sup>12</sup>

**Zinecard**—a cytoprotective agent indicated 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/m<sup>2</sup> and who will continue to receive doxorubicin therapy to maintain tumour control.<sup>15</sup>

**Cardioxane**—indicated in adults for the prevention of chronic cumulative cardiotoxicity caused by anthracycline use in advanced and/or metastatic breast cancer patients who have received a prior cumulative dose of 300 mg/m<sup>2</sup> of doxorubicin or a prior cumulative dose of 540 mg/m<sup>2</sup> of epirubicin when further anthracycline treatment is required.<sup>16</sup>

Despite the absence of randomised controlled trials directly comparing dexrazoxane with alternative interventions such as surgery, two non-randomised clinical studies have been conducted, which formed the basis of its licence. These trials confirmed extravasation injury using fluoroscopy—a diagnostic approach is not routinely used in many clinical settings.<sup>17</sup> Findings demonstrated that intravenous dexrazoxane was highly effective in preventing tissue necrosis, with 98.2% of patients avoiding surgical procedures. The treatment was generally well tolerated, with only mild, transient adverse effects reported, such as local discomfort or sensory

changes. Notably, 71% of patients were able to resume SACT without interruption, supporting the practical utility and safety of dexrazoxane in oncology care.<sup>17</sup>

Confirming an extravasation injury remains clinically challenging. Diagnosis is typically based on a combination of clinical judgement and presenting symptoms such as pain, swelling and erythema—features that can closely resemble common local reactions to SACT. Furthermore, existing clinical trials have not captured patient perspectives on the management of extravasation, and this aspect remains under-represented in the literature. Notably, a previously published systematic review on the topic did not include any studies examining patient experience during extravasation management.<sup>18</sup>

Harrold *et al* conducted a systematic review on the management of cytotoxic chemotherapy extravasation and identified significant variation in clinical practice across settings, with a lack of robust, high-quality evidence to support standardised protocols.<sup>18</sup> Most of the included studies were retrospective, small in scale and methodologically limited, resulting in no clear consensus on the most effective management strategies. Notably, the review highlighted a critical absence of patient-reported outcomes in the literature, leaving a gap in understanding the patient experience of extravasation and its management.

The systematic reviews that have been carried out have primarily focused on specific interventions or drug classes, such as the use of topical treatments, hyaluronidase or surgical techniques, often reinforcing the finding that the evidence base remains weak and heterogeneous. Moreover, none of the reviews have offered a comprehensive synthesis of the clinical efficacy of dexrazoxane, despite its widespread licensure and high cost. Key gaps identified across reviews include the continued reliance on non-randomised or observational data, a lack of standardised outcome measures and minimal inclusion of patient-centred endpoints.<sup>2,3,6,8,13,14,19–25</sup>

This review seeks to evaluate the clinical efficacy of dexrazoxane in the management of anthracycline extravasation, with the aim of informing evidence-based practice and supporting rational, equitable decision-making in oncology care. By systematically assessing current evidence, we aim to clarify the role of dexrazoxane, identify any remaining gaps in the literature and make recommendations for future research and clinical guidelines.

Consequently, the aim of this review is to evaluate the clinical efficacy of dexrazoxane in the management of anthracycline-induced extravasation.

*Clinical efficacy is defined as the absence of lasting tissue damage or the need for surgical intervention in patients.*

Four key objectives were established to achieve the overall aim of this study. The first objective was to determine whether patients required surgical intervention following dexrazoxane administration. The second was to assess whether deviations from the currently licensed use of dexrazoxane had any impact on clinical efficacy. The third objective focused on summarising alternative

**Table 1** Items included in data extraction table

Paper details	► Date of paper ► Year of paper ► Main author
Setting	► Public or private ► Country
Regimen information	► Regimen used ► Time of administration ► Route of administration ► The cycle number ► Anthracycline used ► Peripheral or central route of administration ► Type of cancer
Administration information	► Any previous incidence of any drug extravasation ► How often patient observed
Extravasation information	► Site of extravasation ► Size/volume of extravasation
Risk factors for extravasation	► Age ► Comorbidities ► Site of cannula
Dexrazoxane use	► Availability of dexrazoxane ► Doses ► Times from incident first administered ► Was regimen given as per licence (gap between doses)
Further management of extravasation	► If surgery was carried out and date ► Additional therapies as well as dexrazoxane to manage extravasation
Outcomes of patient	► Surgery needed ► Loss of limb
Details of follow-up	► Free text

therapies employed in the management of anthracycline-induced extravasation. Finally, the study aimed to report patient outcomes where such data were available.

## MATERIALS AND METHODS

### Search strategy and selection criteria

This systematic review was conducted in accordance with recognised methodological guidance for evidence synthesis, including predefined eligibility criteria, independent screening and structured data extraction. It was reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.<sup>26</sup> The review protocol was registered on the PROSPERO, an international systematic review registry (CRD42024611046) on 7 November 2024.

### Information sources and search strategy

Studies were identified through a literature search, guided by the Population, Intervention, Comparison, Outcomes (PICOs) framework,<sup>27</sup> using MEDLINE, EMBASE and Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases, from 1 January 2000 to 30 June 2024 corresponding to the period following the licensing of dexrazoxane for extravasation

and to include relevant trial data preceding its approval. The complete, database-specific search strategies for MEDLINE, EMBASE and CINAHL, including all search terms, Boolean operators, controlled vocabulary (MeSH, Emtree and CINAHL Headings), and applied limits for language, age group and publication dates, are provided in online supplemental file 1. Reference lists of review articles were scrutinised to identify additional relevant publications.

Article screening was conducted in two phases according to predefined inclusion criteria. Initially, two independent researchers (PC and KK) screened titles and abstracts following the removal of duplicates. Subsequently, full-text articles were assessed by four of the research team, with 10% of these full texts independently double-screened by two additional researchers, distinct from the initial screeners. Any discrepancies or uncertainties arising at either screening stage were resolved through consensus discussion among all researchers.

Studies were eligible for inclusion if they were published in English and involved human participants aged 18 years or older who received dexrazoxane for the treatment of extravasation, resulting from SACT containing an anthracycline. Eligible study designs included reference lists from systematic reviews as well as randomised controlled trials, observational studies and case or cohort reports. Extravasation events related to anthracycline administration via both peripheral and central venous lines were considered. All formulations and brands of dexrazoxane, whether licensed or used off-label, were included. Studies were excluded if they were pharmacological investigations focused solely on drug properties or effects. Additionally, book reviews, opinion pieces, editorials and articles published only as abstracts were excluded.

### Data extraction process

A standardised data extraction form was developed and independently piloted by two researchers using a random sample of two articles to ensure consistency and reliability. For each included article, the data that were extracted are found in table 1.

### Quality assessment

The methodological quality and risk of bias of the included studies were assessed using the Joanna Briggs Institute (JBI) critical appraisal tools.<sup>28</sup>

### Analysis

Eligible studies included in the final analysis were thoroughly reviewed, and relevant data were extracted into a standardised Excel data extraction table developed for this review. Key characteristics of each study were synthesised, and findings were summarised accordingly. Quantitative data from the extraction table were presented as descriptive summaries. Additionally, qualitative information collected beyond the extraction table was analysed using the PICO framework.<sup>27</sup> Thematic analysis was guided by our research

questions, focusing on the necessity of surgical intervention, dexrazoxane dosing and administration, alternative therapies employed and patient outcomes. A full meta-analysis was not conducted due to the limited number and generally low quality of available studies (eg, case studies), which would render any pooled estimates statistically unreliable and potentially misleading. Because of heterogeneity across study designs, outcomes and measures, a quantitative meta-analysis was not feasible. Therefore, we followed the *Synthesis Without Meta-analysis* reporting guideline to structure and transparently report our narrative synthesis.<sup>29</sup>

### Patient and public involvement

There was no patient or public involvement in this systematic review.

## RESULTS

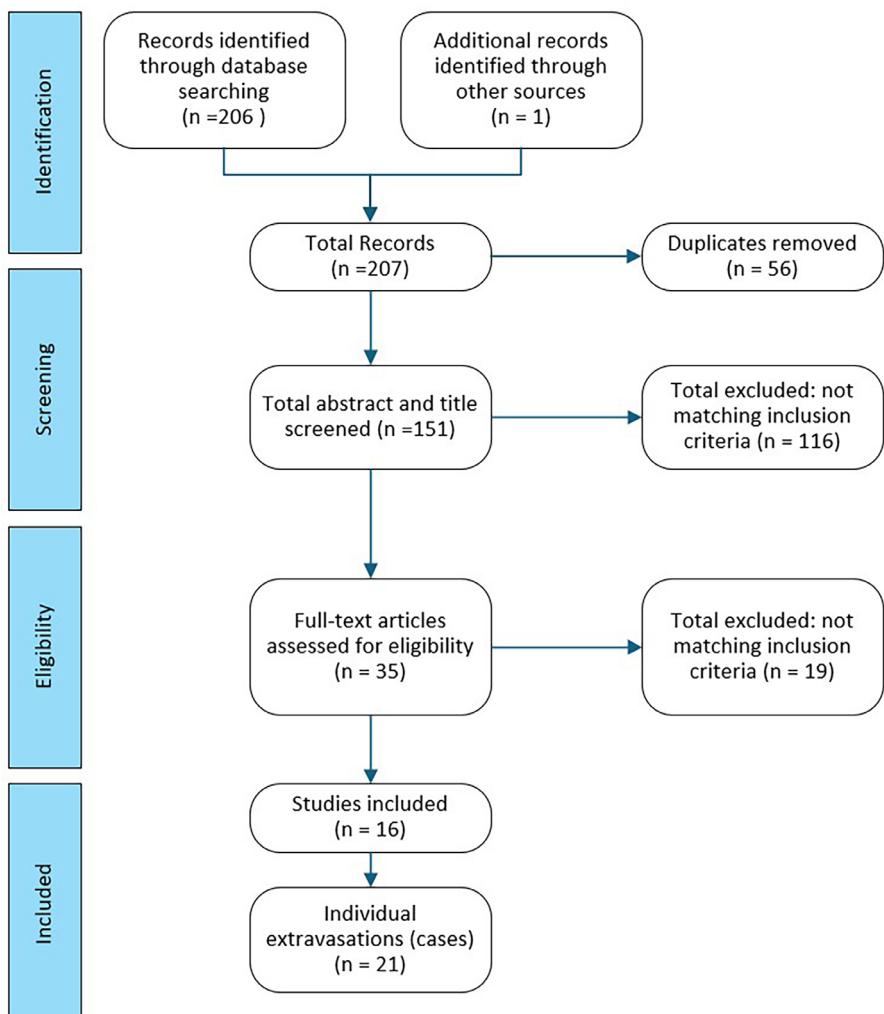
### Article screening and description of included studies

The initial database search retrieved 207 articles, of which 56 duplicates were removed. After screening by title and abstract, a further 116 articles were removed.

Following the full paper review, 19 were excluded. A total of 16 articles were included in the final analysis. Full details of exclusions are given in [figure 1](#). All included studies involved extravasations. Most reports originated from Europe (n=10) with four from America, one each from Australia and Lebanon ([table 2](#), full data available in online supplemental file 2). This review identified 16 articles that reported 21 individual cases of anthracycline extravasation, primarily through case reports or case studies.<sup>30-45</sup>

### Description of extravasation

The majority of reported extravasations was caused by epirubicin<sup>30-32 40 42 43 45</sup> (n=10) followed by doxorubicin and doxorubicin-emch (Albumin-bounded product)<sup>34 35 38 39 41 44</sup> (n=7) and liposomal doxorubicin (pegylated and non-pegylated)<sup>36 37</sup> (n=3) ([table 2](#), full data available in online supplemental file 2). There was an isolated case of extravasation caused by mitoxantrone.<sup>33</sup> The most common cancer type being treated was breast cancer using fluorouracil, epirubicin and cyclophosphamide with or without docetaxel. Where recorded, none of the patients in each study had previously had an



**Figure 1** PRISMA flowchart. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

**Table 2** Results from extraction for extravasations

ID	Anthracycline used	Peripheral/central	Site of extravasation	Dexrazoxane given as per licence	Surgery carried out and date	Loss of limb reported
FROST2006 <sup>35</sup>	Doxorubicin	Peripheral	Near left carpal joint.	No	No surgery reported	No
CONDE-ESTEVEZ 2010 <sup>31</sup>	Doxorubicin	Peripheral	Injection site: median basilic vein at the right antecubital fossa	Yes	No surgery reported	No
ROE2011 <sup>36</sup>	Epirubicin	Peripheral	Right wrist	Yes	No surgery reported	No
MUTHURAMALINGAM 2013 <sup>38</sup>	Epirubicin	Peripheral	Local swelling, left hand	Yes	No surgery reported	No
MUTHURAMALINGAM 2013 <sup>38</sup>	Epirubicin	Peripheral	Unknown	Yes	No surgery reported	No
MUTHURAMALINGAM 2013 <sup>38</sup>	Epirubicin	Peripheral	Local swelling, redness and complained of pain.	Yes	No surgery reported	No
ROE 2011 <sup>39</sup>	Epirubicin	Peripheral	Dorsum of right hand	Yes	No surgery reported	No
AGNER 2014 <sup>26</sup>	Epirubicin	Peripheral	Right arm	No	Multiple abrasions of bullae were performed by plastic surgeon as well as superficial necrectomies.	No
JENSEN2003 <sup>36</sup>	Epirubicin	Peripheral	Right cephalic vein	Not documented	No surgery reported	n/a
ARROYO 2010 <sup>27</sup>	Epirubicin	Peripheral	Right antebrachial basilic vein	No	No surgery reported	No
BOS 2001 <sup>28</sup>	Epirubicin	Peripheral	Dorsal surface of the left hand	Not documented	No surgery reported	No
FROST2006 <sup>35</sup>	Doxorubicin-emch	Peripheral	Not specified but photo of left forearm	No	No surgery reported	No
DEVOS2012 <sup>33</sup>	Liposomal doxorubicin	Peripheral	The patient complained of pain around the intravenous access site, which rapidly spread to the left axilla. A closer examination showed painful oedema of the whole arm and axilla.	No (not within 6 hours)	No surgery reported	No
CHANG2020 <sup>29</sup>	Mitoxantrone	Peripheral	Right forearm	Doses and specific days of treatment not documented.	Three surgeries were performed at 5 weeks (eschar excision), 6 weeks (fascial excisional debridement) and 8 weeks (definitive skin grafting).	No
TYSON2010 <sup>40</sup>	Doxorubicin	Central	Port in the chest	Yes	No surgery reported	No

Continued

Table 2 Continued

ID	Anthracycline used	Peripheral/central	Site of extravasation	Dexrazoxane given as per licence	Surgery carried out and date	Loss of limb reported
El-SAGHIR2004 <sup>34</sup>	Doxorubicin	Central	Port-a-cath poly site catheter was inserted into her left subclavian vein	Yes	3 months after extravasation, whitish necrotic discharge from another 2 mm split of the surgical scar from the entry site of the port-a-cath chamber. At 4 months, the patient had surgery to remove further tissue necrosis and the catheter.	No
CHANG2016 <sup>30</sup>	Doxorubicin	Central	Pleural cavity	Not documented	Surgical washout	n/a
KAZAKOVA 2021 <sup>37</sup>	Doxorubicin	Central	Intrapleural	No	No surgery reported	N/a
UGES 2006 <sup>41</sup>	Epirubicin	Central	Intrapleural	Yes	Ten days after the end of 3-day therapy the patient developed fever not responding to antibiotics. CT scan revealed thoracic empyema with a trapped lung. Surgical decortication of the lung, with excision of the parietal and visceral pleura, was performed.	N/a
CURTTT2012 <sup>32</sup>	Non-pegylated liposomal doxorubicin ( <i>Mycet</i> )	Central	CVAD	Not documented	No surgery reported	No
CURTTT2012 <sup>32</sup>	Pegylated liposomal doxorubicin ( <i>Caelyx</i> )	Central	CVAD	Not documented	Surgical washout	No
CVAD, Central Venous Access Device.						

extravasation event. Most patients received their anthracycline via a peripheral line<sup>30–33 35 37 39 40 42 43</sup> with seven patients receiving the anthracycline via a central infusion port.<sup>34 36 38 41 44 45</sup>

The site of extravasation varied depending on the venous access device used. For cases where the anthracycline was administered via a peripheral line, extravasation sites involved the hand, wrist and forearm, whereas where the anthracycline was administered via a central line extravasation sites occurred within the pleural cavity.

#### Surgical interventions

Six (29%) cases had surgical interventions,<sup>30 33 34 36 38 45</sup> two of which were surgical washouts.<sup>34 36</sup> Two of the cases, where the anthracycline was administered peripherally, involved debridement, skin grafting and treatment for bullae and superficial necrotomies.<sup>30 33</sup> One case also had necrotic tissue removed at the site of the central port.<sup>38</sup> The remaining case required extensive surgery for a thoracic empyema with a trapped lung.<sup>45</sup>

#### Use of dexrazoxane within licence

Only two healthcare settings out of 16 reported difficulties in obtaining dexrazoxane.<sup>31 44</sup> In one case, the patient was transferred to another hospital.<sup>44</sup> In the second case, the branded dexrazoxane, *Cardioxane* was used.<sup>31</sup> *Cardioxane* is used for the prevention of chronic cumulative cardiotoxicity caused by anthracyclines and therefore is unlicensed for use in extravasation.<sup>16</sup> Only 11 (52%) of the extravasation cases were administered dexrazoxane as per the licensed dose reported in the literature provided by the manufacturer.<sup>10</sup> Five cases (24%) reported administration of dexrazoxane with different dosing schedules compared with the manufacturer's recommendation.<sup>23 34 39 41</sup> One case reported only administering one dose,<sup>32</sup> three cases did not provide full details on administration<sup>33 36 40</sup> and one case did not administer within the recommended 6 hours after the incident.<sup>37</sup> The final case did not follow the manufacturer's recommendations reported use of *Cardioxane*.<sup>31</sup>

#### Additional/alternative interventions used

There was a wide variety of additional interventions used. For pain relief, non-steroidal anti-inflammatory drugs, paracetamol and lidocaine patches were used as well as steroids. One case required fentanyl and a ketamine infusion.<sup>34</sup> Local cooling was applied prior to dexrazoxane in other cases.<sup>30–33 42 43</sup> Dimethylsulfoxide and topical steroids were also used. Intravenous antibiotics were administered, and in three cases, aspiration of the drug was attempted.<sup>31 36 44</sup>

#### Patient outcomes

None of the patients lost a limb, but due to study design limitations, we cannot confirm if outcomes would have differed if other treatments were used. All patients fully recovered, with recovery periods ranging from days to

months. Seven cases (33%) resumed their next SACT cycle as documented.<sup>31 32 39–41 44 45</sup>

There was no difference between the length of recovery when comparing cases where dexrazoxane was administered as per the manufacturer's recommendations and those administered via other dosing schedules. Longer recovery periods were reported for cases in which surgery was required as part of treatment.<sup>30 33 38</sup>

#### Risk of bias assessment (JBI critical appraisal checklist for case reports)

In some cases, the patient demographics, history and diagnostic tests or assessment methods were not clearly described. Despite this, all articles were categorised as low risk of bias.<sup>28</sup>

The certainty of the evidence is low, as all included studies were case reports or case series.

## DISCUSSION

This review identified 21 published cases of anthracycline extravasation, the majority of which involved epirubicin administered via peripheral venous access devices. Dexrazoxane was administered according to the approved dosing schedule in 11 of the 21 cases (52%). Several cases documented deviations from the licensed regimen, including alternative dosing schedules, use of *Cardioxane*, administration of a single dose, incomplete information regarding treatment details and delays in administration beyond the recommended 6-hour window. While product sheets suggest a narrow window for dexrazoxane efficacy, this recommendation is based on animal data, not confirmed through human studies.<sup>46</sup>

A diverse array of adjunctive interventions was described, including analgesia ranging from simple analgesics to opioid infusions, topical therapies, local cooling, aspiration of extravasated fluid and antibiotic administration. This variation highlights the complex, multimodal approach often required to manage extravasation injuries and underscores the ongoing lack of standardised management protocols. Moreover, disparities in dexrazoxane availability and in healthcare professionals' understanding of its appropriate application may help explain the global inconsistency in its use and the varied adjuvant interventions used.

The necessity for surgical intervention further emphasises the critical importance of prompt diagnosis and timely initiation of appropriate treatment. Among the reviewed cases, surgical management remained necessary in 29% (n=6) of cases despite receiving dexrazoxane, ranging from superficial debridement and washouts to complex procedures such as lung decortication for pleural cavity extravasations. These findings highlight that while dexrazoxane may reduce the extent of tissue damage, surgery remains necessary in specific circumstances. This may be relevant where recognition of extravasation may be delayed or for more complicated presentations.

Overall, patient outcomes were favourable across the cases reviewed: no patients experienced limb loss, and all recovered fully, with 33% of cases (n=7) resuming SACT. However, recovery times varied, with some patients requiring extended follow-up and staged surgical interventions. These findings reinforce the importance of prompt recognition and coordinated multidisciplinary management,<sup>47</sup> while also highlighting persistent gaps in standardisation and the need for more robust evidence to guide best practice. Enhancing patient education to improve timely reporting of extravasation signs and symptoms may further optimise outcomes and reduce the risk of complications.

These results are broadly consistent with earlier systematic reviews and observational studies that support dexrazoxane's effectiveness as the only licensed antidote for anthracycline extravasation.<sup>18</sup> However, given the small sample size, case heterogeneity and lack of comparator data, definitive conclusions regarding the causal impact of dexrazoxane on outcomes cannot be drawn. Importantly, no patient who received dexrazoxane experienced loss of limb function; however, the impact on patient care and experience has not been extensively researched and further exploration in the area would be warranted. In two instances, treatment was delayed or altered due to unavailability—either requiring patient transfer or the use of unlicensed preparations.<sup>31,44</sup> This raises questions about equity of access and the influence of local and national regulatory and procurement systems on patient outcomes. Exploring the shared use of dexrazoxane, with cost-sharing arrangements among closely geographically placed organisations to ensure timely administration, may present an alternative strategy to help mitigate the financial burden, as suggested by Tyson and Gay.<sup>44</sup>

Previous literature, including Harrold *et al*, has emphasised the lack of standardised protocols and limited high-quality evidence.<sup>18</sup> Little progress has been made towards robust, prospective or standardised retrospective evidence since 2015. Given the ethical and logistical barriers to conducting controlled trials in this setting, case reports and observational studies remain essential sources of evidence to guide management strategies. However, there has been limited research investment in this area.

This review provides a valuable synthesis of rare and underreported clinical events. It is one of the few reviews to collate global case-level data on anthracycline extravasation, offering insights into real-world practice across diverse healthcare settings. However, the certainty of the evidence is low, as all included studies were case reports or case series—which are inherently prone to publication bias, with limited methodological rigour. Incomplete documentation, particularly regarding dexrazoxane dosing, timing of administration and patient outcomes, further limited the ability to draw firm conclusions. Additionally, the absence of comparator groups prevents any causal inference about the effectiveness of dexrazoxane or other interventions. Despite these limitations,

this review provides an important synthesis of existing evidence, contributing to the broader understanding of extravasation management and underscoring the need for prospective, standardised data collection to strengthen the evidence base.

There is a clear need for the establishment of international registries or prospective observational studies to systematically collect data on extravasation events, treatments administered and patient outcomes. This would facilitate more robust evidence generation and support the development of consensus guidelines not only around the immediate treatment of extravasations with dexrazoxane but also the need for any adjunctive treatments.

Patient experience of the management of extravasation was not included within previous trials and in this review, which could be an area to explore to improve patient outcomes. Institutions should ensure protocols are in place for early recognition and rapid response to extravasation events.

## CONCLUSION

This systematic review highlights the variability in the recognition, management and reporting of anthracycline extravasation, with dexrazoxane frequently but inconsistently used across published cases. While all patients ultimately recovered and many avoided extensive surgical intervention, the diversity in dosing practices, timing of administration and supportive measures reflects an ongoing lack of standardisation in clinical practice. Healthcare professionals' understanding of the appropriate administration of dexrazoxane, or its availability within healthcare systems, may contribute to this variation.

Given the small number of cases, the predominance of anecdotal reports and the absence of comparative data, definitive conclusions regarding the specific impact of dexrazoxane on clinical outcomes remain limited. These findings underscore the importance of timely diagnosis and coordinated multidisciplinary management, regardless of the pharmacological approach employed.

Future research should prioritise prospective data collection, develop consistent reporting standards and explore patient-reported experiences to better inform practice.

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**Contributors** All authors conceptualised the study and led the methodology design. AC registered on PROSPERO, and all authors conducted data collection and analysis. MD drafted the initial results, AC drafted the initial manuscript. All authors reviewed and approved the final manuscript. AC is the guarantor of the work and accepts full responsibility for the integrity and accuracy of the study.

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