Successful dexrazoxane treatment of a potentially severe extravasation of concentrated doxorubicin

David Conde-Estévez[a], Silvia Saumell[b], Antonio Salar[b] and Javier Mateu-de Antonio[a]

Dexrazoxane is now authorized for the treatment of anthracycline extravasations. Several clinical cases of doxorubicin extravasation treated with dexrazoxane have been reported to date, but detailed cases have not been published. We report a case of a successful dexrazoxane treatment for a potentially severe extravasation of concentrated doxorubicin. We also describe objective outcome of this treatment, drug tolerance to dexrazoxane and long follow-up. A 29-year-old man diagnosed with Hodgkin's lymphoma was prescribed a regimen including 90 mg of doxorubicin in a 50 ml infusion using a reduced occlusion infusion pump. After this infusion, the patient complained of pain around the site of injection and presented a 10 × 6-cm swollen area with erythema and inflammation. A significant portion of doxorubicin was extravasated. Dexrazoxane was prescribed as an antidote. Side effects of dexrazoxane were restricted to reversible hematological toxicity, nausea, and vomiting. The next day, the inflammation of the extravasation area was reduced. On day 7, a painless mild induration in the extravasated area was the only remaining sign of the extravasation. On day 40, an arm nuclear magnetic resonance image showed no focal injuries. At 6-month follow-up, the patient has no sequelae. The two risk factors that could have increased the severity of the extravasation are the use of an infusion pump and the high drug concentration. Dexrazoxane proved to be effective and moderately well tolerated. A dexrazoxane stock in oncological facilities could help to promptly handle emergencies like this. Anthracyclines can be administered using reduced occlusion infusion pumps, but it seems preferable to always administer a free-running infusion to minimize accidents like this one. *Anti-Cancer Drugs* **21:790–794**

Anti-Cancer Drugs 2010, **21**:790–794

Keywords: antineoplastic agents, doxorubicin, dexrazoxane, extravasation

Departments of [a]Pharmacy and [b]Hematology, Hospital del Mar (Parc de Salut Mar), Barcelona, Spain

Correspondence to Dr David Conde-Estévez, Department of Pharmacy, Hospital del Mar (Parc de Salut Mar), Paseo Marítimo, 25-29, 08003 Barcelona, Spain
Tel: +34 93 248 38 24; fax: +34 93 248 32 56;
e-mail: dconde@hospitaldelmar.cat

Received 31 March 2010 **Revised form accepted** 25 June 2010

Introduction

Extravasation is a potentially serious complication of chemotherapy by intravenous administration. Its adverse effects include tissue necrosis, compartment syndrome, infection, ulceration, and total or partial loss of limb function, and it can also cause chemotherapy treatment delay. Extravasation injury is an accident in oncology for which the exact incidence is unknown, but it has been reported to occur at rates of 0.1–6% [1,2]. Recent studies found its incidence to be in the lower margin of this range, that is, 0.41% of patients receiving chemotherapy in a study performed in Spain [3] and 0.14% of chemotherapy courses in a study in Japan [4].

Chemotherapy agents may be classified by their potential to cause tissue necrosis when extravasated as vesicants, irritants, and nonaggressive. Vesicant drugs can cause blistering and tissue destruction; irritant drugs can induce pain at the injection site and inflammation without necrosis; and nonaggressive drugs rarely cause any reaction [5,6]. The severity of tissue injury is dependent on the drug concentration and the injected quantity of the chemotherapeutic agent [7].

Anthracyclines are classified as vesicants and their extravasations cause severe tissue damage [5,6]. Doxorubicin extravasation has a reported incidence of up to 6% of infusions, although the actual incidence is probably less than 0.5% [5]. In Spain, this incidence has been considered to be approximately 0.001% of chemotherapy courses after a 4-year study in an oncological reference hospital [3].

Once an extravasation is suspected, a suitable specific treatment should be initiated to avoid its devastating consequences [7]. To date, the management of anthracycline extravasations has included general unspecific recommendations such as stopping the infusion immediately and attempting to withdraw extravasated fluid from extravascular space [8], and additional specific measures such as the local application of ice packs and dimethyl sulfoxide (DMSO) [6,9]. Recently, dexrazoxane has been approved as an intravenous antidote for the management of anthracycline extravasation by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMEA) [10,11]. As extravasation is sufficiently uncommon, therefore, a controlled trial in patients is not

0959-4973 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e32833d9032

feasible and even unethical [8]. For this reason, literature addressing doxorubicin extravasation management is limited to animal studies, case reports, and small human studies. Most of these have not reported objective outcomes and have brief descriptions of the evolution and adverse events. We present a case of successful dexrazoxane treatment of a potentially severe extravasation of concentrated doxorubicin. We also report objective outcome of this treatment by nuclear magnetic resonance (NMR), detailed drug tolerance to dexrazoxane, and 6-month follow-up.

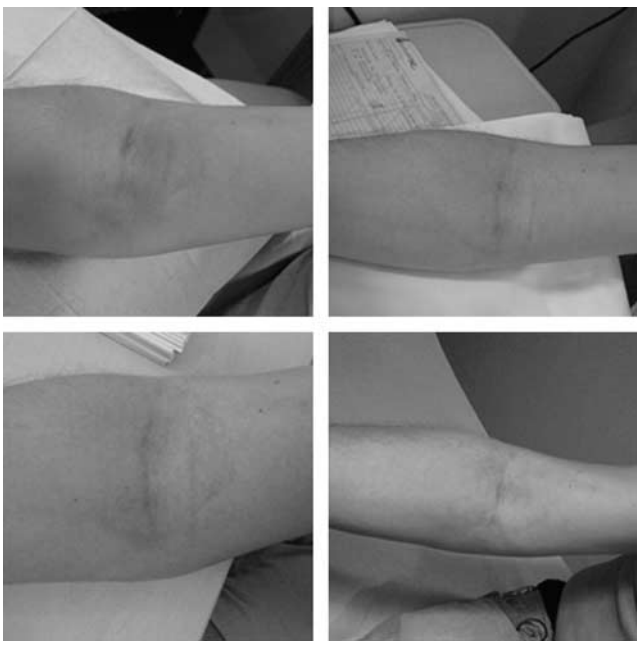
Case report

A 29-year-old man was diagnosed with stage III-B, bulky mass, nodular sclerosis classical Hodgkin's lymphoma in March 2009. Initially, the patient underwent three different chemotherapy regimens. First, he was treated with doxorubicin, bleomycin, vinblastine, dacarbazine (last cycle on 7 May 2009); second with dexamethasone, cisplatin, and cytarabine (last cycle on 14 July 2009); and third with one course of gemcitabine and oxaliplatin. He had disease progression and was therefore scheduled on ifosfamide and etoposide chemotherapy (cycle 22–25 July 2009). Subsequently, the patient underwent successful hematopoietic stem cell mobilization resulting in 10.94×10^6 CD34$^+$ cells/kg to perform an autologous transplantation. Subsequently, the patient had further disease progression and a new regimen was prescribed: bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, and prednisone (escBEACOPP). The first course of escBEACOPP was administered by peripheral intravenous injection into the median basilical vein at the right antecubital fossa using a reduced occlusion infusion pump (Hospira Plum A + Volumetric Infusion Pump, Hospira, Lake Forest, Illinois, USA). The nurse checked the intravenous access site before starting the infusion of each agent and did not detect any abnormality in any case. A 50 ml infusion of 90 mg of doxorubicin for over 30 min was the last treatment of the course. The concentration of the infused doxorubicin was 1.8 mg/ml. The administration was uneventful. After the doxorubicin infusion, the patient complained of moderate pain around the site of injection. The attending nurse suspected an extravasation. General unspecific measures to treat extravasations were taken immediately as per our protocol: the nurse removed the needle, elevated the limb and called a physician. On clinical examination, the patient had an approximately 10×6-cm swollen area with erythema, redness, and inflammation. The exact volume of fluid extravasation could not be determined, but it is likely that a significant portion of the doxorubicin dose was extravasated according to the infiltrated area observed. Dexrazoxane was then prescribed as the specific antidote. The dexrazoxane treatment consists of a 1–2 h infusion (1000 mg/m^2 within 6 h of extravasation on day 1, 1000 mg/m^2 on day 2, and 500 mg/m^2 on day 3) for over 3 days injected into the opposite limb to that of the extravasation incident. Our patient's surface area was 1.94 m^2 and therefore he received 1940 mg of dexrazoxane once a day for 2 days and 970 mg on the third day. Neither cold compress nor DMSO was applied. The first dexrazoxane dose was infused 2.5 h after the extravasation occurred. Blood tests were performed to control renal and hepatic function, and hematology toxicity (Table 1). On day 2, the patient complained of nausea and vomiting classified as grade 2 according to the National Cancer Institute Common Terminology Criteria for Adverse Events requiring granisetron and dexamethasone. On clinical examination, the inflammation of the extravasation area was reduced and no ulceration was observed (Fig. 1). The second dose of dexrazoxane was administrated without incident. On day 3, the patient reported better control of nausea and the last dose of dexrazoxane was also injected without incident. On day 7, there was neither erythema nor ulceration, but only a painless mild induration in the area (Fig. 1). Tests for liver and renal function remained within normal limits. However, grade 2 anemia and thrombocythemia were observed. On day 12, the extravasated site

Table 1 Evolution of hematological tests data after dexrazoxane administration

Hematological tests	Reference range	Day 1	Day 7	Day 12	Day 40
Hemoglobin	13–17 g/dl	9.4	8.1	7.1	10.6
Leukocyte count	$4–11 \times 10^3/\mu l$	8.2	1.3	1.0	10.6
Neutrophil count	$2.5–8.2 \times 10^3/\mu l$	7.7	1.2	0.5	9.2
Lymphocyte count	$1.5–5 \times 10^3/\mu l$	0.3	0.2	0.3	0.5
Platelet count	$150–450 \times 10^3/\mu l$	202	70	8	184

Fig. 1



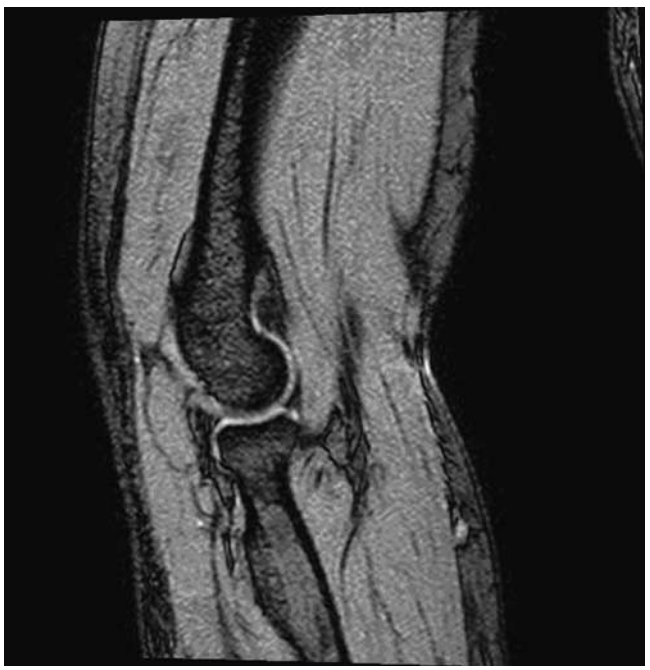
Macroscopic aspect of the lesion on days 1, 2, 7, and 40 after doxorubin extravasation.

remained stable, but the anemia and the thrombocythemia worsened to grades 3 and 4, respectively (Table 1). For this reason, a packet red cell transfusion and a platelet transfusion were prescribed. A week later, blood cell counts were at normal limits and no further transfusion was required. On day 40, blood cell counts were stable (Table 1). From the start of dexrazoxane treatment to the present, there has been no liver, renal or electrolyte dysfunction. The patient had only mild skin pigmentation with a slight induration in the extravasation site and occasional difficulty in moving the arm without impairment of the limb (Fig. 1). To evaluate possible inadvertent sequelae, an arm NMR was performed on day 40 after extravasation, and showed no focal injuries in any of the subcutaneous adipose tissue, skeletal muscle, and skeletal bone layers (Fig. 2). Finally, the patient underwent an autologous transplantation without incident. At 6-month follow-up, the patient remained stable and had no sequelae. However, the patient has had a relapse and has been scheduled for a new chemotherapy regimen.

Discussion

This case describes the successful management of concentrated doxorubicin solution with dexrazoxane confirmed by NMR and without sequelae at 6-month follow-up. The dexrazoxane tolerance was acceptable, with the main adverse effects being transient hematological toxicity, nausea, and vomiting.

Fig. 2



One of the nuclear magnetic resonance (NMR) images on day 40 after extravasation.

Dexrazoxane is a bisdioxopiperazine now authorized for the intravenous treatment of anthracycline extravasation, but was previously authorized by the FDA and the European Medicines Agency for reducing the incidence and severity of doxorubicin-associated cardiomyopathy in women with metastatic breast cancer treated with this anthracycline [12]. The mechanism by which dexrazoxane diminishes tissue damage after anthracycline extravasation is unclear, but a dual mechanism has been postulated. The drug could act as a specific catalytic inhibitor of DNA topoisomerase II, and as an iron chelator of free radicals [13].

The results from clinical case reports and clinical trials have shown that dexrazoxane is highly effective in preventing surgery after doxorubicin extravasation (Table 2). In these clinical trials, only one patient out of the 54 assessable patients (1.9%) required surgical resection [14]. It is worthy of note that doxorubicin was the anthracycline involved in 23 cases (42.6%). The follow-up was limited to the 90th day after extravasation [14]. In addition, one patient of the four cases reported needed surgical intervention [14–17].

Dexrazoxane-adverse events were mild and similar to those of anthracyclines [14]. This fact makes it difficult to elucidate the contribution of dexrazoxane to these adverse events, as both anthracycline and antidote share the same toxicity spectrum. In our case, the escBEACOPP treatment has reported thrombocytopenia and anemia grade 3–4 of 36 and 27%, respectively [18]. The most commonly reported laboratory abnormalities for dexrazoxane were hematological because of the suppression of bone marrow function [14]. Dexrazoxane, in the phase II and III studies, presented grade 3–4 toxicity of white blood cell counts in 46% of cases, grade 3 thrombocytopenia in 21.3% of cases, and grade 3 anemia in only 2.5% of the cases [14]. Our patient presented with grade 3 anemia and grade 4 thrombocytopenia. As he received the whole cycle of chemotherapy and, in addition, dexrazoxane as an antidote, the expected hematological toxicity of escBEACOPP and dexrazoxane could have been additive and increased the severity. Other important adverse events reported in these trials included injection site reactions observed in 27.5% of patients, nausea and vomiting observed in 26.3% of patients [14,15], and transient elevation of liver enzymes occurring in almost one-quarter of the cases. In spite of not observing such liver toxicity in our patient, it seems advisable to monitor liver markers after dexrazoxane treatment. In our case all adverse events were reversible.

Few clinical cases of extravasation of doxorubicin treated with dexrazoxane have been reported to date (Table 2). Most of these cases have not reported objective outcomes, measuring efficacy by the need for surgery within a short period of follow-up. Detailed reporting of adverse events and patient evolution were absent in most cases.

Table 2 Summary of reports using dexrazoxane for doxorubicin extravasation

Reference	Design	Patients (*N*)	Amount of extravasated doxorubicin	Additional therapy	Efficacy	Follow-up
Langer *et al.* [15]	Editorial	1	149 mg	None	No surgery	3 months
El-Saghir *et al.* [16]	Case report	1	NA	GM-CSF	Ulceration + surgery	3 months
Frost *et al.* [17]	Case report	2	30 mg 20 mg	None	No necrosis	23 days 45 days
Mouridsen *et al.* [14]	Prospective	23	NA	None	One patient surgery	3 months

GM-CSF, granulocyte-macrophage colony-stimulating factor.

Langer *et al.* [15] briefly reported a doxorubicin extravasation with dexrazoxane without further details. El-Saghir *et al.* [16] presented the only case treated with dexrazoxane that required surgical resection and local administration of granulocyte-macrophage colony-stimulating factor for proper healing of the ulceration 3 months later. In that case, the failure of dexrazoxane therapy could be related to the concomitant use of DMSO. Later, it was proved that the addition of topical DMSO reduced the efficacy of dexrazoxane based on the results of animal studies [19] and now the concomitant use of both antidotes is contraindicated [10,11]. It is noteworthy that local cooling with ice packs, the other classical specific measure for anthracycline extravasations [9], should be removed from the extravasation area at least 15 min before the dexrazoxane administration to allow sufficient blood flow [10,11,13]. The last two cases of the successful treatment with dexrazoxane were reported briefly by Frost *et al.* [17] with a follow-up of 23 and 45 days, respectively.

In our case, two risk factors could have increased the severity of the extravasation. First, the drug was administered using an infusion pump. General infusion pumps are not recommended for infusing chemotherapy into peripheral veins [8]. However, a special type of pump known as the reduced occlusion pressure pump, can be used to infuse cycles of chemotherapy, including anthracyclines [20]. This pump has a variable occlusion pressure that can be adjusted to its minimum level that causes the pump to signal when pressure is higher. In our case, the nurses did not detect a pump alarm. This is a very rare but possible event. The more probable cause might be because of some pore in the vein, which resulted from repeated punctures. This situation makes it impossible for the pump system to detect any higher pressure. Several extravasations warnings using similar pumps have been reported to the FDA's Manufacturer and User Facility Device Experience (MAUDE) adverse event report system. In one case an extravasation of paclitaxel using the same pump model involved in our case was reported (available at website *http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfMAUDE/search.CFM*).

Second, the drug was concentrated and the more concentrated the injected chemotherapeutic agent is, the more severe the injury would be if extravasated [7]. The concentration of the infused doxorubicin was 1.8 mg/ml, at the higher level of the recommended range. Usually, doses of doxorubicin of less than 100 mg should be mixed in 50–1000 ml of normal saline so that the final concentration ranges from 0.1 to 2 mg/ml [21].

In summary, dexrazoxane has proved to be objectively effective, moderately well tolerated, and without sequelae in a long follow-up as a successful specific treatment in the case of concentrated doxorubicin extravasation. A dexrazoxane stock in oncological facilities could help to promptly handle emergencies like this. Anthracyclines can be administered using reduced occlusion infusion pumps, and to minimize accidents like this it seems preferable to always administer a free-running infusion.

Acknowledgements

The authors thank Isabel Cabot for editorial assistance with the manuscript.

There is no support to be declared.

References

1 Langer SW, Sehested M, Jensen PB. Treatment of anthracycline extravasation with dexrazoxane. *Clin Cancer Res* 2000; **6**:3680–3686.
2 Ener RA, Meglathery SB, Styler M. Extravasation of systemic hemato-oncological therapies. *Ann Oncol* 2004; **15**:858–862.
3 Alfaro-Rubio A, Sanmartin O, Requena C, Llombart B, Botella-Estrada R, Nagore E, *et al.* Extravasation of cytostatic agents: a serious complication of oncological treatment. *Actas Dermosifiliogr* 2006; **97**:169–176.
4 Watanabe H, Ikesue H, Yoshida M, Yamamoto N, Sakamoto S, Koga T, *et al.* Protection against the extravasation of anticancer drugs by standardization of the management system. *Hosp Pharm* 2008; **43**:571–576.
5 Goolsby TV, Lombardo FA. Extravasation of chemotherapeutic agents: prevention and treatment. *Semin Oncol* 2006; **33**:139–143.
6 Reeves D. Management of anthracycline extravasation injuries. *Ann Pharmacother* 2007; **41**:1238–1242.
7 Schrijvers DL. Extravasation: a dreaded complication of chemotherapy. *Ann Oncol* 2003; **14** (**Suppl 3**):iii26–iii30.
8 Mullin S, Beckwith MC, Tyler LS. Prevention and management of antineoplastic extravasation injury. *Hosp Pharm* 2000; **35**:57–74.
9 Bertelli G, Gozza A, Forno GB, Vidili MG, Silvestro S, Venturini M, *et al.* Topical dimethylsulfoxide for the prevention of soft tissue injury after extravasation of vesicant cytotoxic drugs: a prospective clinical study. *J Clin Oncol* 1995; **13**:2851–2855.
10 Kane RC, McGuinn WD Jr, Dagher R, Justice R, Pazdur R. Dexrazoxane (Totect): FDA review and approval for the treatment of accidental extravasation following intravenous anthracycline chemotherapy. *Oncologist* 2008; **13**:445–450.
11 Dexrazoxane. European Medicines Agency, EMEA. Product information: Savene-H-C-682-N-004. Available from *http://www.ema.europa.eu/humandocs/Humans/EPAR/savene/savene.htm*. [Accessed February 11, 2010].
12 Cvetkovic RS, Scott LJ. Dexrazoxane: a review of its use for cardioprotection during anthracycline chemotherapy. *Drugs* 2005; **65**:1005–1024.

13 Hasinoff BB. The use of dexrazoxane for the prevention of anthracycline extravasation injury. *Expert Opin Investig Drugs* 2008; **17**:217–223.
14 Mouridsen HT, Langer SW, Buter J, Eidtmann H, Rosti G, De Wit M, *et al.* Treatment of anthracycline extravasation with Savene (dexrazoxane): results from two prospective clinical multicentre studies. *Ann Oncol* 2007; **18**:546–550.
15 Langer SW, Sehested M, Jensen PB, Buter J, Giaccone G. Dexrazoxane in anthracycline extravasation. *J Clin Oncol* 2000; **18**:3064.
16 El-Saghir N, Otrock Z, Mufarrij A, Abou-Mourad Y, Salem Z, Shamseddine A, Abbas J. Dexrazoxane for anthracycline extravasation and GM-CSF for skin ulceration and wound healing. *Lancet Oncol* 2004; **5**:320–321.
17 Frost A, Gmehling D, Azemar M, Unger C, Mross K. Treatment of anthracycline extravasation with dexrazoxane: clinical experience. *Onkologie* 2006; **29**:314–318.
18 Diehl V, Franklin J, Hasenclever D, Tesch H, Pfreundschuh M, Lathan B, *et al.* BEACOPP, a new dose-escalated and accelerated regimen, is at least as effective as COPP/ABVD in patients with advanced-stage Hodgkin's lymphoma: interim report from a trial of the German Hodgkin's Lymphoma Study Group. *J Clin Oncol* 1998; **16**:3810–3821.
19 Langer SW, Thougaard AV, Sehested M, Jensen PB. Treatment of anthracycline extravasation in mice with dexrazoxane with or without DMSO and hydrocortisone. *Cancer Chemother Pharmacol* 2006; **57**:125–128.
20 NHS Purchasing and Supply Agency. Evaluation report: hospira plum A+ volumetric infusion pump. CEP 07014. 1 October 2007. [*www.pasa.nhs.uk/pasa/Doc.aspx?Path=%5BMN%5D%5BSP%5D/NHSprocurement/CEP/Infusionpumps/CEP07014.pdf*]
21 McEvoy GK, Snow EK, Miller J, Kester L, Welsh OH. *AHFS drug information*. Bethesda, MD: American Society of Health-System Pharmacists; 2010.