

# Extravasation: a dreaded complication of chemotherapy

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## Introduction

Most chemotherapeutic agents are given by intravenous administration, although some drugs are available orally. When given intravenously, these drugs cause few side-effects at the site of injection. However, when they are injected or leak into the surrounding tissues, a tissue reaction varying from irritation to necrosis may arise.

In this article, a patient with extravasation is described and a review of the literature is given.

## Case report

A 69-year old woman was treated for a high-grade soft tissue sarcoma of the leg by resection and radiotherapy. One year later, she developed lymph node and lung metastases. Since her general condition was excellent, a palliative chemotherapy with doxorubicin was proposed. The patient agreed to the treatment and she was admitted to the Department of Medical Oncology for her first treatment.

Doxorubicin at a dose of 75 mg/m<sup>2</sup> was given by intravenous injection. The nurse who had to administer the drug placed a butterfly needle in the right hand and injected the drug slowly. During the injection, the patient did not complain of pain. After administering the drug, the patient said she felt an excruciating pain in her hand. The nurse removed the needle and called a physician. On clinical examination, the woman had a slight redness of the right hand without other signs. A local anti-inflammatory ointment was applied to the hand and the patient was hospitalised.

The next day, she complained of pain and the hand was swollen and red. A small ulceration had developed. The diagnosis of extravasation was made and a local treatment with dimethylsulfoxide (DMSO) was applied three times daily. The patient was treated with analgesics. A surgeon was consulted who suggested observation. After a week, necrosis of the skin developed with exposure of the muscles and ligaments. The wound was treated with sterile dressings. After 6 weeks a skin graft was placed over the wound.

A subcutaneous device was then put in place and doxorubicin treatment continued. After two cycles, there was a partial response and the patient was treated with six cycles of chemotherapy.

She sued the department for medical fault.

## Discussion

Extravasation is one of the most dreaded complications when administering chemotherapy. It is defined either as the escape of a chemotherapeutic agent from a vessel into the surrounding tissues

by leakage or as an involuntary injection of a drug into the tissues. The frequency of extravasation in adults is considered to be between 0.1% and 6%.

The severity of tissue injury is dependent on the type and concentration of the chemotherapeutic agent and the quantity injected. Cytotoxic agents may be classified as irritants or vesicants (Table 1).

Irritants are drugs that can cause an inflammatory reaction, aching, swelling, pain or phlebitis at the injection site or along the vein. They may cause sclerosis and hyperpigmentation along the vein, burning, local warmth, discomfort, erythema or tenderness. These symptoms are self-limiting and there are no long-term sequelae.

Vesicants are drugs that may cause severe and lasting tissue injury and necrosis. Symptoms may arise immediately after extravasation or appear after several days or weeks. Patients may complain of pain or local burning at the infusion site, mild erythema, itching or swelling. Over time, the symptoms of erythema and pain may increase and a discoloration and induration of the skin, dry desquamation or blistering may develop. In case of a significant extravasation, necrosis, eschar formation and ulceration with involvement of underlying tissues may occur. The indolent ulceration lacks granulation tissue formation and there is little peripheral re-epithelisation.

## Prevention of extravasation

The most important approach to extravasation is prevention. Prevention of extravasation takes into account several factors.

- In all departments where cytotoxic agents are given, written guidelines for handling cytotoxic agents and procedures in case of extravasation should be present. In addition to these guidelines, an extravasation kit, with all the necessary material and drugs to treat extravasation, should be present [1]. There should also be a form to report the extravasation to the authorities (hospital direction, legal department, nursing department).
- Persons responsible for administering cytotoxic drugs should be informed and educated about the drugs and the problems they may cause in case of extravasation and the procedures to follow if this happens.
- A cytotoxic agent should not be administered in an extremity if within the previous 48 h there was venopuncture above the place of insertion of the catheter.
- For vesicant drugs, the placement of a subcutaneous device before the start of chemotherapy is advisable; in case of infusions of longer duration (e.g. more than 1-h infusions), the placement of a subcutaneous device is obligatory.

**Table 1.** Vesicants and irritants

DNA-binding vesicant drugs	
Alkylating agents	Nitrogen mustard
Anthracyclines	Daunorubicin, doxorubicin, epirubicin, idarubicin
Others	Dactinomycin, mitomycin C
Non-DNA-binding vesicant drugs	
Vinca alkaloids	Vinblastine, vincristine, vinorelbine
Taxanes	Docetaxel, paclitaxel
Irritant drugs	
Alkylating agents	Carmustine, dacarbazine, carboplatin, cisplatin, cyclofosfamide, ifosfamide, melphalan, oxaliplatin, thiothepa
Antimetabolites	Cytarabine, fludarabine, 5-fluorouracil, gemcitabine, raltitrexed, methotrexate
Others	Irinotecan, bleomycin, etoposide

- Drugs should never be administered using a butterfly needle, and even in case of a bolus injection or a short infusion, a catheter has to be inserted into a vein. Small and fragile veins should be avoided. The catheter should never be inserted in a limb that is affected by lymphoedema or has a neurological weakness. Veins adjacent to tendons, nerves or arteries should be avoided, while areas of high venous pressure should not be used.
- If the drugs are given by slow bolus injection by peripheral infusion, the placement of the catheter should be in the forearm and not in the hand. In case of extravasation, the tissues and muscles in the forearm may prevent involvement of ligaments, nerves and bone.
- Before administering a cytotoxic agent, the catheter is flushed by a free flowing infusion with sodium chloride 0.9% or glucose 5% solution for at least 5 min. At the end of the administration of a cytotoxic drug, the same procedure is repeated.
- The patient is informed that in case of pain or other discomfort the nurse should be informed immediately.
- The exact position of the catheter is checked by aspiration of blood. The drug is then slowly injected. In case of complaints by the patient, the administration is stopped, the nurse aspirates as much as possible of the injected drug, stops the infusion, leaves the catheter in place and calls for a physician [1].
- The physician gives instructions how to deal with the event and may start treatment for extravasation. The event and the treatment procedure should be noted in the patient file and on the extravasation form.

### Treatment of extravasation

The type of treatment for extravasation is dependent on the drug.

- In case of extravasation of an irritant, the catheter may be removed and the affected extremity is elevated. Cold or warm compresses may be applied. Hot packs are believed to cause vasodilatation, leading to the dilution of the extravasated drug. Cold packs may cause venous constriction leading to localization of the drugs and therefore increase degradation of toxic metabolites. They may also reduce local inflammation and pain.
- Inflammation may be treated with local anti-inflammatory drugs. Pain should be treated by analgesics.

- In case of extravasation of a vesicant, the catheter is left in place and an antidote may be injected depending on the extravasated drug. Furthermore, the affected extremity is kept elevated and a cold or hot pack is applied. In case of extravasation with vinca alkaloids, a hot pack is applied, since in animal models there was an increase in ulceration when cold packs were applied. For all other vesicants cold packs are indicated.

### Anthracyclines

Several drugs have been tested in the treatment of anthracycline extravasation in animal models or patients.

#### Prevention of damage

Until recently, the application of topical DMSO has been advocated for the treatment of extravasation of anthracyclines. Several animal experiments [2, 3] and case reports have described the efficacy of intradermal or topical DMSO [4].

In a prospective study, 17 patients were treated with topical DMSO. It was applied immediately after extravasation covering twice the area affected by the extravasation. This treatment was repeated twice daily for 14 days. No ulceration developed and no surgical intervention was necessary [5].

In another prospective study, 69 patients suffering from anthracycline extravasation had 99% DMSO applied topically every 8 h for 7 days in combination with intermittent cooling (1 h, three times daily). This treatment proved to be safe and effective with ulceration developing in only one patient. Side-effects were mild local burning and a characteristic breath odor due to DMSO [6].

Recently, dexrazoxane has been advocated for the treatment of anthracycline extravasation. In animal models, the use of one single subcutaneous injection of dexrazoxane after an injection of doxorubicin, daunorubicin or idarubicin reduced the tissue lesion significantly, with a reduction in the size of the wound and the healing duration. Dexrazoxane could be administered up to 3–6 h after anthracycline extravasation without loss of efficacy. Triple dosage of dexrazoxane appeared to be more effective than a single dose [7].

This treatment was also tested in two patients with epirubicin extravasation. Both patients were treated intravenously with dexrazoxane (1000 mg/m<sup>2</sup> within 5 h of extravasation on day 1, 1000 mg/m<sup>2</sup> on day 2, 500 mg/m<sup>2</sup> on day 3). No surgical intervention was necessary and no long-term sequelae were seen after 3 months. The only side-effects were transient elevation of liver transaminases and leukopenia [8].

Experimental animal studies have been performed with vitamin C [3, 9], heparin fractions [10], hyaluronidase [11], *N*-acetylcysteine [12] and  $\alpha$ -tocopherol [13] showing a beneficial effect of all these drugs in the prevention of anthracycline-induced ulceration. However, their value in patients remains to be determined.

### Treatment of ulcerations

If injury occurs, the patient may develop ulceration with a raised, red, painful edge and a necrotic yellow base. These ulcers lack granulation tissue and there is very little peripheral epithelial ingrowth. They do not heal and tend to increase in size and depth.

In animal experiments, it was shown that the injection of granulocyte-macrophage colony-stimulating factor (GM-CSF) 6  $\mu$ g at the injection site of doxorubicin had a beneficial effect on the doxorubicin-induced tissue necrosis [14]. This beneficial effect was confirmed in another animal model for granulocyte colony-stimulating factor (G-CSF) or GM-CSF [15].

One patient has been reported who developed two doxorubicin-induced ulcerations. One ulcer was treated with weekly GM-CSF at a dose of 400  $\mu$ g subcutaneously for 3 weeks and did heal by the fourth week. The second ulcer was treated with G-CSF, but no improvement was seen [16].

The use of hyperbaric oxygen therapy was also studied in animal models. While hyperbaric oxygen treatment did potentiate doxorubicin toxicity when administered concomitantly [17], it had a beneficial effect on ulcer healing when given twice daily compared with no hyperbaric treatment [18]. To date, the value of this approach in patients with ulcerations due to extravasation has not been published.

In patients with ulcerations due to anthracycline extravasation, two surgical approaches are possible. One surgical treatment option is to perform early extensive surgical debridement within 24 h to 1 week after extravasation with delayed closure of the wound [19, 20]. Pain is an indication for immediate surgery [21]. The extent of surgery may be determined by fluorescence microscopy. Excision of all fluorescence-positive tissues led to less late sequelae when performed within seven hours [22]. The wound may be temporarily covered with a biological dressing. Once the wound is clean, a delayed application of a skin graft (split-thickness) may be applied after 2–3 days [21].

Most surgeons opt for a conservative approach since only one-third of vesicants will give rise to ulceration. However, continued swelling, erythema and pain without ulceration, persisting after conservative therapy or the presence of large areas of tissue necrosis or skin ulcerations are indications for surgery [23–26]. In this case, surgery is usually performed 2–3 weeks after extravasation.

## Mitomycin C

Mitomycin C is a vesicant [27]. Contrary to anthracyclines, distant and delayed ulcerations have been described [28–30]. As for anthracyclines, toxicity of mitomycin C can be prevented by the topical application of DMSO [31, 32]. Also, a topical mixture of DMSO (90%) and  $\alpha$ -tocopherol (10%) was effective in the prevention of skin ulceration by mitomycin C [33]. There is also a report that local injection of pyridoxine may slow or prevent necrosis and alleviate pain [34]. In case of ulceration due to extravasation, preoperative magnetic resonance imaging (MRI) may be used to indicate the extent of tissue invasion [35].

## Taxanes

Both docetaxel and paclitaxel have been reported to cause tissue damage after extravasation. Several reports indicate that docetaxel may cause erythema, blistering and pain. Conservative management resulted in complete recovery after 4 weeks in one patient [36], while the dilution with subcutaneous saline, local hypothermia and topical DMSO (three times every 45 min), corticosteroids or diclofenac were effective in restricting inflammation [37, 38].

In animal models, paclitaxel gave rise to skin ulceration and necrosis proving its vesicant character. A treatment with intradermal hyaluronidase (15 U) diluted in saline was effective in preventing paclitaxel-induced ulceration. Topical treatment as topical DMSO, cooling or heating did not had a beneficial effect [39].

Several case reports have reported on the vesicant character of paclitaxel [40–43]. No guidelines for treating paclitaxel extravasation in man have been proposed.

## Vinca alkaloids

Vinblastine, vincristine and vinorelbine cause tissue damage after extravasation and are classified as vesicants. Animal experiments showed that cold packs may increase toxicity, while hot packs may limit skin damage. Also, the use of calcium leucovorin, diphenhydramine, hydrocortisone, isoproterenol, sodium bicarbonate and vitamin A cream were ineffective in animal models [44].

In humans, dilution of the drugs with saline or hyaluronidase (150–1500 U subcutaneously in surrounding tissues) in combination with hot packs is the treatment of choice [1, 44].

## Nitrogen mustard or mechlorethamine

Nitrogen mustard is a vesicant that produces severe and prolonged skin ulceration after extravasation. In several animal experiments, sodium thiosulfate was not able to prevent nitrogen mustard skin toxicity when given intravenously immediately before or after extravasation. However, when given immediately after extravasation by intradermal injection, it had a protective effect.

Therefore, in humans the recommendation in case of nitrogen mustard extravasation is an immediate subcutaneous adminis-

**Table 2.** Guidelines for antidote use after extravasation

Drug	Antidote	Advice
Anthracyclines	DMSO	Apply locally as soon as possible and repeat every 8 h for 7 days
	Dexrazoxane	1000 mg/m <sup>2</sup> i.v. within 5 h of extravasation on day 1, 1000 mg/m <sup>2</sup> on day 2, 500 mg/m <sup>2</sup> on day 3
	Ice packs	
Mitomycin C	DMSO	Apply locally as soon as possible and repeat every 8 h for 7 days
Nitrogen mustard	Sodium thiosulfate	2 ml of a solution of 4 ml sodium thiosulfate + 6 ml sterile water for injection s.c.
Vinca alkaloids	Hyaluronidase	150–1500 U s.c.
	Hot packs	

DMSO, dimethylsulfoxide; i.v., intravenously; s.c., subcutaneously.

tration of 2 ml of 0.17 M sodium thiosulfate solution (4 ml of 10% sodium thiosulfate and 6 ml sterile water for injection) [26].

## Conclusion

Extravasation is a severe complication of chemotherapy. Prevention by adequate guidelines of chemotherapy administration and training of nurses is of the utmost importance. In case of extravasation, the correct treatment according to the specific drug should be given (Table 2).

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