Extravasational toxicity of anticancer chemotherapy and its management

A Thakur1, JS Thakur2*

Abstract
Introduction
Anticancer drugs have a number of side effects, including toxic effects on bone marrow, kidney, lymphoreticular tissue, mucosa and cochlea. Extravasational toxicity is a complication of anticancer drugs, unmentioned in the majority of clinical textbooks other than oncology, explaining why residents may be unaware of this preventable catastrophe. The objective of this paper is to review and present the clinical features and management of extravasation of these anticancer drugs so that first line staff get acquainted to this complication and its management. After reading this paper, residents and clinicians will be more vigilant in anticancer drug infusion and management of extravasation.

Conclusion
Once extravasation occurs, tissue injury is inevitable but can be reduced with the proper antidote. A trained member of staff should administer this, preferably from the oncology department only.

Introduction
As the incidence of cancer is increasing, cancer management has become a team effort consisting of family members, physicians, surgeons, radiations and medical oncologists, psychiatrists and physiotherapists.

The objective of this team is to provide a cure or palliation with minimal side effects and quality of life to the patient.

Radiation therapy has become target-orientated to avoid injury to normal tissue but now chemoradiation is the preferred modality. In spite of giving promising results, these anticancer drugs have a number of side effects, which include toxic effects on bone marrow, kidney, lymphoreticular tissue, mucosa and cochlea. In India, the oncology department is overloaded with cancer patients; hence, anticancer drugs are being infused in the parent departments by nurses and residents. However, extravasational toxicity is one of the dreaded complications of anticancer drugs, which did not find a place in the majority of clinical textbooks other than oncology, and hence many of the residents may be unaware of this preventable catastrophe.

The incidence of extravasations in adults is 0.1% to 6.5%. Extravasation can occur in any centre and even in highly advanced oncology centres, but these advanced centres have specially trained oncology-nursing staff. Commonly, chemotherapy is infused in clinical or parental departments of the patient, and work of infusion is left to a house surgeon or an intern, who may not have yet acquired a reasonable experience in venepuncture. Even the resident may not have adequate knowledge of the measures to be undertaken in case of extravasation due to absence of this complication and its management in the majority of clinical textbooks.

The objectives of this paper are to review and present the clinical features and management of extravasation of these anticancer drugs so that the first line staff gets acquainted to this complication and its management.

Discussion
The authors have references some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki (1964), and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects gave informed consent to participate in these studies.

Classification based on mode of tissue injury
Extravasation of anticancer drugs causes tissue damage by different mechanisms: (a) DNA-binding drugs are initially absorbed locally causing direct cell death. Later, the drug is released from the nearby dead cells and causes further damage in surrounding tissue. (b) Non-DNA-binding drugs are metabolized and cleared early; thus, tissue damage is less and easily neutralized by the antidote.

On the basis of extravasational toxicity, anticancer drugs are classified as irritants or vesicants (Table 1).

Vesicant drugs: They cause blister formation, tissue death and ulcer formation at extravasation site.

Irritant drugs: They act as irritants on the injection site, and pain is the main symptom. Ulcer formation is rare but extravasation of large amount can lead to ulceration.
Table 1 Vesicant and irritant chemotherapeutic drugs

<table>
<thead>
<tr>
<th>Vesicant drugs</th>
<th>Irritant drugs</th>
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<tbody>
<tr>
<td><strong>Alkylating agents (DNA-Binding):</strong> Methotrexate (Methotrexate)**</td>
<td><strong>Alkylating agents:</strong> Cyclophosphamide, Ifosfamide, Melphalan, Carmustine, Dacarbazine, Thiotepa</td>
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<tr>
<td><strong>Antitumour antibiotics (Anthracyclines, DNA-Binding):</strong> Mitomycin C, Daunorubicin (Rubidomycin), Doxorubicin (Adriamycin), Epirubicin, Idarubicin, Actinomycin D (Dactinomycin)</td>
<td><strong>Antimetabolites:</strong> Methotrexate, 5-Fluorouracil (5-FU)*, Cytarabine (Cytosine arabinoside), Fludarabine, Gemcitabine</td>
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<tr>
<td><strong>Vinca alkaloids (Non-DNA Binding):</strong> Vinorelbine</td>
<td><strong>Antitumour antibiotic:</strong> Bleomycin</td>
</tr>
<tr>
<td><strong>Taxanes (Non-DNA Binding):</strong> Docetaxel, Paclitaxel</td>
<td><strong>Epipodophyllotoxin:</strong> Etoposide*</td>
</tr>
<tr>
<td><strong>Platinum analogs:</strong> Cisplatin*, Carboplatin, Oxaliplatin*</td>
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**Highly vesicant, * Low vesicant.

Guidelines for infusion of cytotoxic drugs

Institutional policy

There are specific guidelines for infusion of anticancer drugs15,17–21, but the institutes or hospitals should also have their own policy on chemotherapy infusion. The attending physician and nursing staff should be familiar with the anticancer drug and its complication. The infusion should be given at the time of maximum staff strength and care. The ward should have information charts displayed both for staff and patient22. All the antidote drugs should be at the bedside of the patient. Patient should be informed about the symptoms of extravasation and its complications, and explained that despite best efforts, extravasation can occur22. All extravasation incidences should be brought to the notice of the department and institutional oncology board. They can review the case and decide on further management of the patient and preventive measures.

Intravenous access

This is the most important step in the prevention of extravasation. First of all, assess the general condition and age of the patient. Patient with paralysis, sensory deficit, tracheostomy or impaired higher mental function needs extra care due to inability to alert the staff during extravasation23. Elderly patients have increased risk of extravasation due to fragile veins. Similar risk is involved with deep veins, previous infusion within 48 h, multiple attempts for venous access, radiation or regional lymph node clearance of the limb15,22.

The second most important step is to decide on central or peripheral intravenous access. Commonly, peripheral intravenous access is preferred. However, drugs to be given longer than 1 h should be administered only via a central line15,23,24. The flexible intracatheter devices should be used, as other rigid devices have a tendency for vessel injury8,15. Forearm is the preferred site due to catheter stability and muscle protection for the nerve and tendons in the event of extravasation, which is inevitable in case of access on hand or wrist3. Venous access should be secured in a single attempt and in case of failure, the site should be changed to another proximal vein. The device should be covered with transparent dressing so that the signs of extravasation are visible to the patient and staff. Intravenous access should be checked by running normal saline intravenously. This step immediately confirms extravasation and also hydrates the patient, a prerequisite for chemotherapy. Now, anticancer drugs are started, and the patient is instructed to alert the attending staff if there is any pain, itching, stoppage of infusion or oedema in the limb.

Clinical features of extravasation

Extravasation of cytotoxic drugs leads to stoppage of infusion, and the patient will complain of excruciating pain and itching in the infusion site. Within a few hours, the extravasation area will show erythema, oedema and induration. Without intervention, these sign and symptoms will increase, and skin will show discolouration and desquamation of epidermis or blister formation in a few days. Extravasation of a large dose of cytotoxic drug leads to ischaemia and ulcer formation (Figure 1).

Management of extravasation

- **Immediate bedside management:** Immediate management of extravasation reduces the tissue injury, and morbidity is inevitable if this step is delayed. On extravasation, infusion of drug should be stopped at once and normal saline infusion should be started. In case of an irritant drug, intravenous cannula should be removed while it is left in place in case of vesicant drug and proper antidote should be given15. The limb is elevated, and cold pack is applied to the local site. Hot packs are applied in extravasation of vinca alkaloids, as it causes vasodilatation and diffusion of the drug from the site. Parenteral strong analgesics help in the reduction of inflammatory reaction and its symptoms.

- **Use specific antidotes:** There are a number of studies and case reports in literature8,10,18,25–45 to show...
the efficacy of various antidotes for extravasation of anticancer drugs.

a) Dimethylether sulfoxide (DMSO):  This drug is applied topically in case of extravasation of anthracyclines and mitomycin C. 1–2 ml of 1 mM 50%–99% DMSO is applied to the effective area thrice a day for 1–2 weeks. Oliver et al.25 used topical DMSO every 6 h for 14 days in 20 patients with extravasation of anthracycline and in a follow-up of 16 patients for 3 months; no patient developed skin ulceration or necrosis. Bertelli et al.27 used 99% DMSO topically every 8 h for 7 days in 127 patients with various vesicant drugs, and only one patient had skin ulceration.

b) Hyaluronidase:  This drug breaks hyaluronic acid and increases the permeability of connective tissue and hence the diffusion of extravasated drug.10,15,24 It is recommended in vinca alkaloids, epipodophyllotoxin and taxanes26,31 extravasations. It is injected through the existing cannula or subcutaneously in a clockwise manner if cannula has been removed. About 1–6 ml of 150 U/ml hyaluronidase is sufficient, but its dose corresponds to the amount of extravasated drug.

c) Dexrazoxane:  It is a recent FDA-approved antidote for anthracycline extravasation. Exact mechanism of action is unknown but some evidences suggest reversible topoisomerase II inhibition and binding to iron, which prevents the formation of free radicals responsible for tissue injury.22,32 It is infused slowly over 1–2 h in a large vein other than the injured vein in a dose of 1 gm m⁻² within 6 h of extravasation, and repeated again on the second day with the same dose and 500 mg m⁻² on the third day. Based on anecdotal reports, DMSO interacts with dexrazoxane and decreases its efficacy; therefore, concurrent use should be avoided.32 Fever, fatigue, gastrointestinal disturbances, headache, transient elevation of liver transaminases and decrease in blood count are a few of the side effects.

d) Sodium thiosulfate:  This drug is indicated in extravasation of mustine HCl and cisplatin. Its exact mechanism of action is also unknown, but is thought to chemically neutralize the reactive alkylating species of mustine HCl and decrease the production of hydroxyl radicals.33

e) Miscellaneous drugs:  This group includes drugs with low level of evidence in the management of extravasation of anthracycline. These drugs have shown efficacy in experimental animals only, and include vitamin C24,35, and E.,36,39 heparin fraction41, melatonin42, hyperbaric oxygen.44 Scuderi et al.44 have reported local injection of saline (20–90 ml) with occlusive topical application of corticosteroid to avoid skin necrosis. Local infiltration of hydrocortisone in anthracyline extravasation did not prevent skin necrosis in mice model.45

Surgical intervention:  Surgical intervention is reserved in cases that have not received antidote or presented late with erythema or necrosis. In two studies56,67, saline washout with liposuction prevented skin necrosis, performed within 24 h of various extravasation injuries. This procedure is performed by irrigating the subcutaneous tissue with normal saline through a 4-mm blunt tipped liposuction cannula, and removing subcutaneous tissue with the extravasated drug.

Untreated extravasation leads to skin necrosis and needs plastic surgeon intervention. Surgical intervention involves two approaches48–55. One approach involves extensive surgical debridement preferably under fluorescence microscope within 24 h to 1 week after extravasation and secondary wound closure. The second conservative approach involves daily saline dressing. The wound is then covered with split skin graft or flap. Necrosis of peripheral vessels and nerves of limb may need amputation. However, immediate intervention is indicated in case of non-resolving

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erythema, pain or swelling and presence of large skin defects. Few experimental animal and human studies have reported good results with the use of granulocyte macrophage colony stimulating factor (GM-CSF) in the management of ulcers in anthracycline extravasation\(^1\)\(^{19,56-59}\).

- **Physiotherapy:** It is indicated in late complications (functional or neural loss of the limb), but is rare.

**Conclusion**

Extravasation is a dreaded complication of anticancer drugs and can be avoided through proper guidelines. Once extravasation occurs, tissue injury is inevitable but can be reduced with the proper antidote. All anticancer drugs should be infused by trained staff, and preferably in the oncology department only. The clinical textbooks should cite this complication and its management, so that primary clinical physicians are able to handle this complication in its golden hour.

**References**