Management of extravasation of antineoplastic agents

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Key words: chemotherpy, extravasation, cytotoxic drugs, cytostatic drugs

Table of contents

The following guidelines are based on non-randomised clinical trials (impossible to conduct due to ethical reasons) and on clinical experience and expert opinion — category II–IV of evidence quality and recommendation level A–C.

According to the authors, the guidelines contains the most justified principles of diagnostic and therapeutic procedures. They should, however, be interpreted in the context of the individual clinical situation. Recommendations do not always correspond to the current refund rules in force in Poland. In case of doubt, you should be sure of the current refund possibilities of each procedure.

Introduction

Systemic treatment of cancer patients is very often associated with side effects, which include local reactions due to extravasation of cytotoxic and cytostatic drugs. Extravasations occur in 0.1–7% of all intravenous infusions of cytotoxic drugs, and the frequency of serious sequences is approx. 0.01–1%. The retrospective analysis of MD Anderson shows that in 2002 there were 10 times less extravasations than 15 years earlier (0.01% *vs.* 0.1%) [1–3].

The intensity of reaction after extravasation can differ within a wide range, from mild redness and oedema up to intense, irreversible ulceration, necrosis, and severe pain, most often requiring surgical treatment. Many of these events could be avoided by adherence to preventive principles.

Definition of extravasation

Extravasation is a random and unintentional leakage of intravenously (IV) infused, potentially damaging medications into the tissue around the site of infusion or direct tissue infiltration by misuse of the drug, which can lead to local inflammation, ulcers, and in extreme cases to necrosis [3, 4].

Classification of antineoplastic drugs according to consequences of extravasation

The clinical picture of local lesions varies according to the type of extravasated cytotoxic or cytostatic drug,

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Table 1. Classification of antineoplastic drugs according to consequences of extravasation

Vesicant drugs	
High potential of damage	**Low potential of damage**
DNA binding	Cisplatin (in lower concentrations < 0.5 mg/mL)
Bendamustine	Etoposide in high concentration
Cisplatin (> 0.5 mg/mL)	Fluorouracil (in high concentration)
Dactinomycin	Oxaliplatin
Daunorubicin	
Doxorubicin	
Epirubicin	
Idarubicin	
Mitomycin C	
Mitoxantrone	
Nitrogranulogen	
DNA non-binding	
Cabazitaxel	
Docetaxel	
Paclitaxel	
Trabectedin	
Vinblastine	
Vincristine	
Vindesine	
Vinflunine	
Vinorelbine	

Table 2. Classification of antineoplastic drugs according to consequences of extravasation

Irritant drugs	Non-vesicant drugs
Carboplatin	Aflibercept
Carmustine	Alemtuzumab
Cisplatin	Amifostine
Dacarbazine	Asparaginase
Etoposid	Bevacizumab
Fluorouracil	Bleomycin
Iphosphamide	Bortezomib
Irinotecan	Cetuximab
Ixabepilon	Cladribine
Liposomal daunorubicin	Cyclophosphamide
Liposomal doxorubicin	Cytarabine
Melfalan	Fludarabine
Mitoxantrone	Gemcitabine
Oxaliplatin	Interferons
Streptozotocine	Interleukin-2
Teniposid	Merkaptopurin
Topotecan	Methotrexate
	Monoclonal antibodies
	Octreotide
	Pamidronate
	Pemetrexed
	Raltitrexed
	Rituximab
	Temsirolimus
	Thiotepa
	Trastuzumab

which justifies the division of drugs (Tables 1 and 2) into the following categories:
— vesicant;
— irritant;
— non-vesicant.

Strongly damaging drugs are divided into subgroups of high or low destructive potential as well as DNA-binding and DNA non-binding. Severely damaging drugs can cause intensive inflammatory reactions, blisters, deep damage of tissue surrounding the vessel including necrosis, and severe pain. These symptoms can occur immediately after extravasation, or later: after a few days or even several weeks. Sometimes delayed effects can occur, which may result in disability. Although irritant drugs cause pain or even redness and signs of infiltration, they do not lead to permanent damage and irreversible effects. Non-vesicant medications cause longer lasting local reactions if they penetrate the tissues surrounding the vessel [5].

There is no explicit information on cisplatin, oxaliplatin, and taxanes in the literature, but it is not a mistake to classify the listed drugs as highly destructive and requiring more attention.

Extravasation risk factors

Limiting the consequences of extravasation of cytostatics requires the identification of patients at higher risk and implementation of prophylaxis (e.g. insertion of intravascular port). The risk factors for extravasation include patient-related factors and factors related to the procedure of cytostatic administration [3–7].

Patient-related factors that increase the risk of extravasation are as follows:
— fine and fragile veins;
— thick and/or hardened veins as a result of damage after previous punctures;
— movable veins;
— conditions related to circulatory disorders (e.g. Raynaud's syndrome, diabetes, lymphoedema,

superior vena cava syndrome, circulatory failure, post-radiation damage);
— proneness to bleeding, coagulation disorders;
— obesity;
— impaired peripheral sensation, paresis;
— difficulty communicating with patient (e.g. unconscious or handicapped, small children);
— long-lasting infusion;
— patients' age (elderly patients and children).

Risk factors related to puncture technique and infusion procedure are as follows:
— inexperienced or incompetent staff responsible for drug administration;
— repeated puncture attempts;
— inappropriate site of puncture;
— administration of medications in bolus;
— administration of drugs under high pressure;
— use of improper equipment (e.g. sharp needles, butterfly venous catheters, and others);
— improper protection and fixation of puncture;
— improper insertion of intravascular port;
— damage of an intravascular port.

Prophylaxis of extravasation

If the rules for proper intravenous administration are followed, the risk of extravascular complications can be significantly reduced — prevention is a very important part of the management. In every chemotherapy centre administering cytotoxic and cytostatic drugs, the following rules are necessary [3–6]:

1. Placing in a prominent location the guidelines for handling cytotoxic and cytostatic drugs and management in case of extravasation and use of available rescue kit;
2. Providing a special form for making reports to patient's clinical records and to health authorities and the hospital administration;
3. Employment of specialised and regularly trained (including complications of extravasation) staff responsible for drug administration;
4. The choice of appropriate vascular bed before infusion or injection and avoiding administration of the drugs in vessels located on the dorsal part of the hand and around the joints, because the extravasations that occur in these areas may lead to motor limitation and disability (the forearm area is the most appropriate);
5. Avoiding drug administration in vessels that were punctured over the past 48 hours above the planned site;
6. Administration of highly vesicant drugs by central lines, whenever possible (mandatory for continuous infusions of drugs from this group);
7. Administration of drugs through intravenous cannulas (even — short-term injections), and not by common, sharp needles and needles called "butterflies";
8. Avoidance of administration of drugs to small, friable vessels, and located on limbs with impaired circulation (e.g. on side with lymphadenectomy made), oedema, and neurological paralysis;
9. Avoiding the administration of drugs to venous vessels that are adjacent to tendons, nerves, arteries, and places with high venous pressure;
10. Fixing the cannula or other needles with good visibility of the puncture and with use of transparent fixing dressing;
11. Checking the puncture by flushing with cytostatics is absolutely forbidden;
12. Administration of highly vesicant and irritant drugs as the first ones;
13. Administration of drugs mentioned in point 12 at the concentration indicated by the manufacturer (not higher);
14. Close observation of the injection site during drug administration — patients should be asked for complaints (e.g. pain, burning, swelling, discoloration, and others), and if they occur, drug administration should be immediately discontinued by stopping the infusion, aspirating the largest possible volume of the already administered drug, leaving the cannula in place, and calling the doctor (specialist oncologist);
15. Frequent checking for possible backflow;
16. Flushing a vessel with 10 mL of 0.9% NaCl or 5% glucose prior to drug administration, every 2–3 minutes during the administration by a hand-held device, and always after the end of chemotherapy (flushing a vessel between subsequent medications is always necessary);
17. Taking special care with drug administration in the elderly patients, those with "fragile" vessels, and in children;
18. In case of extravasation, recording the event and treatment in clinical records.

Mechanism of tissue damage by cytotoxic and cytostatic drugs

The mechanism of tissue damage varies, depending on the kind of extravasated drug. The intensity of damage also depends on the concentration and volume of extravasated drug. Mechanisms of tissue damage caused by extravasation of anthracyclines and *Vinca* alkaloids are the best known.

After leakage to surrounding tissues anthracyclines are absorbed by the cells in which they are bound to deoxyribonucleic acid (DNA) and cause direct damage. Then, they are released from cells (endocytolysis), and

enter the adjacent cells, which are also damaged and this leads to their destruction. This process resembles a chain reaction and can last for a long time and cause extensive and deep ulcers, including necrosis. Anthracycline drug molecules may be present in surrounding tissues for several weeks or even months after extravasation. It is important to distinguish extravasation from local hypersensitivity to doxorubicin, which is observed in 3% of adults and 21% of children. Local hypersensitivity is most often manifested by erythematous strip along the vein with or without urticaria. These symptoms disappear after approx. 30 minutes regardless of the treatment.

Drugs that do not bind to DNA (such as *Vinca* alkaloids or podophyllotoxin derivatives) are characterised by a different mechanism of local tissue damage. In this case, the drugs themselves are metabolised, but tissue damage is mainly due to lipophilic substances in which these drugs are dissolved. This kind of extravasation is easier to neutralise [4, 6–9].

Clinical symptoms of extravasation

Extravasations sometimes occur regardless of preventive measures. In general, a highly vesicant drug causes a subcutaneous infiltration, which is most often associated with immediate and intense pain, burning, swelling, and redness. Swelling and painful redness usually develop within a few hours, and tissue infiltration and blisters — within a few days. Necrosis and deep ulcer develop in 7–28 days. Necrosis occurs in approx. 25% of all cases of highly vesicant drugs extravasation. The ulcers never heal spontaneously. Deep necrosis usually includes periosteum, tendon sheaths, and tendons — hence the necrosis is accompanied by very severe pain that requires treatment with strong analgesics including opioids. Necrosis and ulcers must be treated surgically (mainly with skin transplants). Irritants most often cause symptoms of local inflammatory reaction, such as itching, swelling, pain, burning, redness, discomfort, and sometimes local symptoms of phlebitis. These symptoms disappear spontaneously or after anti-inflammatory treatment without long-term effects — apart from symptomatic treatment (cold compresses, higher positioning, anti-inflammatory, and analgesic drugs) they do not require any other management.

The symptoms that may cause suspicion of extravasation include: no blood backflow, discontinuation or slowdown of free infusion, and clear resistance to the syringe plunger during drug administration [3–6].

Differential diagnosis

Some medications can cause local reactions during proper administration, and these reactions resemble extravasation (e.g. hypersensitivity to doxorubicin). The symptoms imitating extravasation include: erythema around the injection site and along the vein ("flare" phenomenon), urticaria, and local itching. Another clinical symptom to be considered during differential diagnosis of extravasation is phlebitis caused by the administered drug. This type of inflammation may occur possibly after thrombosis or vein hardening and cause burning or cramping along the vein.

Topical reactions are caused by: asparaginase, cisplatin, daunorubicin, doxorubicin, epirubicin, fludarabine, nitrogranulogen, and melphalan.

Inflammation of the vein can be caused by: amsacrine, carmustine, cisplatin, dacarbazine, epirubicin, fluorouracil in continuous infusion, especially in combination with cisplatin, gemcitabine, nitrogranulogen, and vinorelbine [3].

Management of extravasation

In cases of extravasation of a cytotoxic or cytostatic drug, the infusion of the drug or its administration by a hand-held device should be immediately discontinued. Before removing the needle from the vessel, one must attempt to aspirate the remaining fluid. If there is an antidote for the drug that was used, it should be given the same route for the most effective neutralisation (do not administer an antidote with high-pressure, to avoid spreading of extravasated drug). In addition, the tissue surrounding the extravasation site should also be injected with antidote. This applies in particular to the use of hyaluronidase. After administration of the antidote, the needle or the cannula should be removed. Then compresses should be used with all patients, and the limb where extravasation occurred should remain in a raised position for at least two days after the extravasation. Limb lifting accelerates reabsorption of the leaked drug by lowering the hydrostatic pressure in the capillaries. Then the limb should be gradually restored to movement with the help of physiotherapy.

The aforementioned algorithm is widely used and accepted. Hyaluronidase is the most commonly used antidote in case of *Vinca* alkaloids and taxane extravasation (recommendation level V, C). Hyaluronidase is an enzyme that degrades hyaluronic acid, increases tissue permeability, and accelerates the absorption of the extravasated substance. In the typical case, 150 units of hyaluronidase should be dissolved in 1 mL of 0.9% NaCl solution and administered directly to the vessel, then a similar dose of the drug should also be dissolved in 1 mL of physiological saline, and the extravasation area should be injected with small volumes (0.1–0,2), changing the needle each time. Most authors recommend to give five injections of 0.2 mL of fluid each. This proce-

dure could be repeated within 3–4 hours. The maximum dose of hyaluronidase used is 900–1500 units. Hyaluronidase is recommended in cases where more than 50% of the planned dose has been extravasated.

Most authors agree on the need for warm compresses to accelerate flow and absorption of the drug ("dilute and attenuate" principle) for extravasations caused by *Vinca* alkaloids and taxanes, and some also recommend similar treatment for extravasation of platinum derivatives, especially oxaliplatin (ESMO-EONS recommendation). Warm compresses are usually used for 15–20 minutes four times a day for the first 24–48 hours or 30–60 minutes immediately after extravasation, and alternating every 15 minutes for at least 24 hours thereafter. There are also instructions that recommend using such packs only for the first four hours.

There is no consensus among experts on how to counteract the most dangerous extravasations of anthracyclines. Many authors as well as the instructions existing in two oncology hospitals (Washington University Hospital in Seattle and Royal Marsden, London) do not recommend the use of any medications when anthracyclines are extravasated, except for the corticosteroids used in Royal Marsden and in many hospitals in the United Kingdom (hydrocortisone 1% ointment). However, there are also publications presenting ineffectiveness or even harmfulness of corticosteroids. The only exception is the recommendation to use oral corticosteroids in case of extravasation of large volumes of oxaliplatin (indicated — 8 mg dexamethasone twice daily for up to 14 days) [10].

It might also be added that the ESMO-EONS, the Oncology Nursing Society in the United States, and the National Institute for Cancer Genetics in Genoa recommend lubrication of areas after anthracyclines extravasation or use of compresses with 50–99% dimethyl sulfoxide (DMSO) — recommendation level IV, B. Dimethyl sulfoxide is a popular solvent that, after application, penetrates the tissues and has the capacity to remove free radicals, and may accelerate the evacuation of the drug from the affected area. After application of the drug to the skin at the extravasation site (if liquid, e.g. four drops per 10 cm^2 of skin surface to an area twice that of extravasation) we wait for the drug to dry without applying the dressing and only then put on a cold compress. DMSO is usually applied every eight hours for at least 7–14 days. DMSO is also used by the aforementioned authors when extravasation occurs during administration of mitomycin C and platinum derivatives [3]. However, the first reports about full DMSO efficacy have not been confirmed by at least three further studies, and one of them has even shown that DMSO given intradermally induced necrosis by itself, while superficial use increased the healing time. Nevertheless, in the 1980s, the clinical benefits of DMSO use in 20 patients with anthracyclines extravasations were demonstrated in a pilot study. In 1995, DMSO efficacy was evaluated in 144 patients with extravasations of different drugs (epirubicin, cisplatin, doxorubicin, ifosfamide, mitoxantrone, carboplatin, mitomycin C, and fluorouracil), and only one patient in this group experienced ulceration after extraction of epirubicin [3, 11, 12]. The side effects associated with the use of DMSO include local burning and redness of moderate intensity as well as unpleasant breath odour, specific for DMSO. Dolbene® gel, containing DMSO, heparin, and dexpanthenol, is available in Poland (solely by the target import procedure) as well as RIMSO 50® — DMSO 50% (50mL vial — target import) and Cryo-Pur® DMSO 100% (syringes with volume of 10, 20, 30, and 50 mL — medical device of class IIa). Our own experience with the use of DMSO gel (Dolbene® gel) at the Maria Sklodowska-Curie Institute — Oncology Center in Warsaw indicates its effectiveness in cases of immediate use after the event, and a small extent of extravasation.

Currently there are many reports in the literature and ESMO-EONS guidelines recommending the use of dexrazoxane in patients after anthracycline extravasation (recommendation level III, B). Dexrazoxane, which is a catalytic topoisomerase II inhibitor, binds and displaces iron from anthracycline-iron complexes, thereby preventing the formation of free oxygen radicals. Dexrazoxane should be administered intravenously, not later than six hours after extravasation, at the dose of 1000 mg/m^2 in the first two days and 500 mg/m^2 on the third day. Also , the use of granulocyte-macrophage colony-stimulating factors (GM-CSFs) and hyperbaric oxygen therapy in cases of anthracycline extravasation should also be mentioned. However, these methods should still be considered as experimental.

In the cases of extravasation of anthracyclines or other drugs (exceptions — *Vinca* alkaloids, taxanes, and platinum derivatives, especially oxaliplatin, where cold compresses increase the severity of neuropathy), it is recommended to use cold compresses (0°) or sometimes even ice (warm packs are harmless). However, there is no agreement as to how the compresses should be used. Some people use cold compresses for 15–20 minutes four times a day for 24–48 hours, others for 30–60 minutes and then alternately every 15 minutes for 24 hours. Cold packs cause vasoconstriction, which leads to a reduction of the drug in the extravasation area, and thus to an increase in the cleavage of toxic metabolites at a given site. In addition, cold compresses can reduce local inflammation and pain.

In cases of extravasations caused by nitrogranulogen, cisplatin, bendamustine, and dacarbazine in high concentrations, the American Oncology Nursing Society recommends the use of sodium thiosulphate (level of recommendation V, C) to neutralise the undesired lo-

Table 3. Recommendation regarding extravasation of vesicant drugs

Drug	Antidote	Management
Amsacrine	Does not exist	
Anthracyclines: (Daunorubicin, Doxorubicin, Epirubicin, Idarubicin)	DMSO	Apply immediately after the event and continue every 8 hours for 7–14 days
	Dexrazoxane	1000 mg/m^2 up to 6 hours after the event for 2 days 500 mg/m^2 on day 3 Cold or ice compress
Cisplatin	DMSO? Sodium thiosulphate	Cold compress
Oxaliplatin	Sodium thiosulphate?	Warm compress
Dactinomycin	Does not exist	
Carmustine	Does not exist	
Melphalan	Does not exist	
Mitomycin C	DMSO	Apply immediately after the event and continue every 8 hours for 7–14 days
Mitoxantrone	DMSO?	As above
Nitrogranulogen Cisplatin Bendamustine Dacarbazine	Sodium thiosulphate	2 mL of solution prepared from 4 mL of thiosulphate and 6 mL of water for injection and/or 2 mL of thiosulphate for each 1 mg of extravasated drug
Streptozotocin	Does not exist	
Taxanes (docetaxel, paclitaxel)	Hyaluronidase	1–6 mL 150–1500 U/mL IV and SC (the most commonly 1 mL a 150 U in 5 doses of 0.2 mL) Warm compress
Vinca alkaloids (vinblastine, vincristine, vinorelbine, vindesine)	Hyaluronidase	1–6 mL 150–1500 U/mL IV and SC (the most commonly 1 mL a 150 U in 5 doses of 0.2 mL) Warm compress

cal effects of these drugs. The rationale is that sodium thiosulphate is a competitive target in the alkylation process — it is used subcutaneously at the dose of 2 mL per milligram of extravasated drug.

If the symptoms (most importantly severe pain) persist despite the aforementioned procedures, the patient should be consulted with the surgeon due to the possible need for surgical therapy including skin transplantation. As mentioned above, ulceration after anthracycline occurs even after minor extravasation, increases covertly (under the scab), is usually deeper than can be judged based on appearance, and shows no tendency to spontaneously heal. Surgical interventions in such patients are therefore essential. Surgical treatment can be used immediately after extravasation or in a deferred mode. If severe pain and infiltration are present from the beginning of extravasation, then surgical excision of the affected area is recommended (assessment of extensity of extravasation under fluorescence microscope is indicated) within one to seven days after the event. However, conservative treatment is most commonly used because there are symptoms of non-healing ulcer and necrotic lesions only in about 25% of extravasations of vesicant drugs. In the case of persistent symptoms (swelling, erythema, extensive infiltration with or without ulceration and accompanying pain), a deferred surgical procedure should be performed, usually in about 2–3 weeks after the event [3–6, 8, 11–18].

Port and other central line-related extravasations

Extravasations of cytostatic or cytotoxic drugs given through the central lines are very rare. Complications were observed only in 0.24% of 815 patients. Complications can be very serious because of the risk of mediastinal inflammation (the extravasated drug can enter the mediastinum, the pleura, or subcutaneously into the chest and neck area). The most common clinical symptom is severe chest pain. Diagnosis of complications is based on clinical symptoms confirmed by computerised tomography (CT) scans of the chest.

Table 4. The contents of the tray with the rescue materials used in extravasations

Materials and medicines	Formula	Amount
Syringes	2 mL	5
	5 mL	5
	10 mL	5
Needles	0.5, 0.6, 0.8, and 1.2	10 pieces each
Sterile dressings	10 × 10 cm	10 pieces
Swabs moistened with alcohol		10 pieces
Waste bags		3
Dolbene® ointment or other DMSO formulas		1 package
Hyaluronidase	150 I.E.	1 package (10 pieces) in a refrigerator
Sodium thiosulphate 20–25%	5–10 mL amp.	2
Dexrazoxane		10 amp. of 500 mg
Water for injection	10 mL	4 amp.
0.9% NaCl solution	10 mL	4 amp.
Ice pack	2	In the freezer
Warm/cold pack	2	On tray

In the case of extravasation, it is essential to stop the infusion and to aspirate as large a volume as possible from the central line. If anthracycline is extravasated, the administration of dexrazoxane to the peripheral vein could be considered. Antibiotics and corticosteroids may be used intravenously, as well as strong analgesics and other medications for the management of mediastinal or pleural inflammation. Conservative treatment is the most commonly used, but in exceptional cases surgical treatment may be used to remove as much as possible of the extravasated drug [3, 17, 18, 20, 21].

Observation after extravasation

It is very important to closely monitor patients after extravasation because clinical symptoms are different and range from mild inflammatory symptoms that occur immediately after extravasation to severe ulcers and necrosis developing slowly and often covertly. ESMO-EONS recommend that such patients be referred for follow-up examinations every day or every two days in the first week after extravasation and then once a week until the lesion is healed [3].

Summary

Management of extravasations of cytotoxic and cytostatic drugs remains controversial. Controlled clinical trials on extravasation cannot be conducted for ethical reasons. Prevention seems to be the most important thing. In the case of extravasations caused by *Vinca* alkaloids and taxanes, hyaluronidase and warm compresses should be used. However, after extravasation of other medicines it is best to use cold compresses. When an anthracycline is extravasated, it is advisable to use DMSO and intravenous dexrazoxane. Ointments or other forms of DMSO are also recommended for use after extravasations of mitomycin and possibly mitoxantrone and cisplatin. The limb should be always immobilised and should remain in a raised position for at least two days. If symptoms persist (especially pain), surgical treatment should always be employed.

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