CLINICAL PRACTICE

Czech Republic consensus on recommendations to prevent and manage extravasation (paravasation) of cytotoxic drugs

Samuel Vokurka*[1], Viktor Manasek[2], Darja Navratilova Hrabankova[3], Simona Sipova[4], Zuzana Sustkova[5], Lenka Turkova[6], Erika Hajnova Fukasova[7], Zuzana Sykorova[8], Sarka Kozakova[9], Jitka Wintnerova[10]

[1] *Department of Oncology and Radiotherapeutics, University Hospital and Faculty of Medicine in Pilsen, Charles University, Czech Republic*
[2] *Complex Oncological Center, Novy Jicin, Czech Republic*
[3] *Department of Hematology, General University Hospital in Prague, 1st Faculty of Medicine, Charles University, Czech Republic*
[4] *Department of Oncology and Radiotherapeutics, University Hospital in Pilsen, Czech Republic*
[5] *Department of Internal medicine, Hematology and Oncology, University Hospital Brno, Czech Republic*
[6] *Internal hematology Clinic, University Hospital Kralovske Vinohrady in Prague, Czech Republic*
[7] *Oncology Clinic, University Hospital Ostrava, Czech Republic*
[8] *Clinic of Comprehensive Cancer Care, Masaryk Memorial Cancer Institute Brno, Czech Republic*
[9] *Pharmacy, Masaryk Memorial Cancer Institute Brno, Czech Republic*
[10] *Department of Paediatric Haematology and Oncology, University Hospital in Motol Prague, Czech Republic*

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ABSTRACT

Extravasation (paravasation) of cytotoxic chemotherapy drugs represents a very important complication in oncology nursing. Prevention and proper care can reduce the risk of extravasation and its consequences. A consensus on chemotherapy extravasation management have been reached within twenty seven oncology and haemato-oncology centres in the Czech Republic. Ensuring reliable, safe venous access, choice of injection site, venous line control, and patient education are integral and very important parts of care. DMSO (99%) is recommended for topical application after extravasation of anthracyclines, mitomycin C and cisplatin. Dry cold should be applied in case of DMSO-treated cisplatin extravasation, anthracyclines, mitomycin C and in extravasations of all other cytotoxic drugs (except for those with recommended dry heat applications). Dry heat is to be applied in cases of extravasation of oxaliplatin, taxanes and vinca-alkaloids. Hyaluronidase applied subcutaneously around the extravasation is recommended in the case of extravasation of taxanes and vinca-alkaloids. Dexrazoxane i.v. can be used when dealing with extravasation of anthracyclines. Corticosteroids applied subcutaneously, moist heat or cooling, are not recommended.

Key Words: Nursing, Chemotherapy, Extravasation, National consensus on recommendations

1. INTRODUCTION

Extravasation (paravasation) of cytotoxic chemotherapy drugs represents a very important complication in oncology nursing. Prevention and proper care can significantly reduce the risk of extravasation and its consequences. To find a consensus and summarise the recommendations for in-

*Correspondence: Samuel Vokurka; Email: samuel.vokurka@gmail.com; Address: Department of Oncology and Radiotherapeutics, University Hospital and Faculty of Medicine in Pilsen, Charles University, Czech Republic.

terventions for daily practice in Czech Republic oncological and haemato-oncological centres, representatives of several national professional groups and societies (Supportive Care Group of the Czech Society for Oncology, Czech Society for Haematology, Oncology Section of the Czech Nurses Association and the Society for Ports and Permanent Catheters) reviewed and discussed individual centres' standards of care, the opinions of the expert groups and the available literature guidelines and recommendations in respect to the Czech Republic's healthcare needs and options in 2019-2020.

2. METHODS

The members of the extravasation working group made every effort to create a written document that defines several procedures and interventions that can be considered as basic and fully feasible for daily practice across all oncology centres across the country.

Cytotoxic drug extravasation written guidelines and recommendations were originally obtained in 11/2018–1/2019 from 11 (out of 27) oncology and haemato-oncology centres in our county. In the period of 2/2019–2/2020 the data were reviewed and compared with the available European Society for Medical Oncology/European Oncology Nursing Society (ESMO/EONS) guidelines,[1] which were considered as the basic independent standard comparator, and missing, incomplete or controversial information was further discussed and compared with other available published literature, papers and the summary of product characteristics (SPC) reports.[1–16] The final version of the document was completed and made by the need for mutual consent of the members of the working group. The final document was further reviewed in 1–3/2020 by members and board members of the above-mentioned professional groups and societies (see Introduction).

The document, in the form of a recommendation for standard care, is not intended to limit the scope of extravasation care which may, in individual workplaces, significantly exceed and extend the scope of the care recommended here.

3. RESULTS

Preventative measures are considered essential to minimise the risk of extravasation and its consequences. Given the length of chemotherapy, the nature of cytotoxic drugs (vesicants, irritants, non-irritants), the route of administration (several hours to several days of continuous administration) and other individual circumstances (e.g. patient cooperation, peripheral vein condition, vascular disease, lymphoedema, obesity) the choice of mid-term and long-term venous access devices, such as peripherally inserted central catheters (PICC) and ports is recommended. PICC may be the optimal option for treatments of up to 3 months, whereas a port is recommended for treatment periods of more than 6 months. For high risk cytotoxic drugs (vesicants i.e. anthracyclines, taxanes, vinca-alkaloids, and irritants i.e. melphalan, ifosfamide, etoposide, 5-fluorouracil, methotrexate, platinum derivatives, irinotecan and topotecan), central vein access devices should be prioritised. Substitution for platelet values of 20-50 x 10^9/l is particularly recommended when introducing central venous access in haemato-oncological patients with thrombocytopenia, especially in the case of puncture of v. subclavia or v. jugularis. PICCs are a very good alternative, allowing the possibility of introduction without prior haematological preparation and eliminating the risk of serious complications (e.g. artery puncture, haemothorax or other severe bleeding).

Peripheral venous entry is not recommended to be inserted in the area surrounding joints, the lower limbs, limbs with lymphoedema or where there is a risk of developing lymphoedema (e.g. after axillary exenteration), at sites of haematomas and inflammation, in a patient with a history of repeated unsuccessful venepuncture or at or distal to sites of previous blood collection and intravenous administration. The palm side of the wrist, veins in the cubital well or dorsal side of the hand should not be used for chemotherapy administration. Individually, in cases of very good vein quality and cooperative patients, it is possible to accept short-term introduction of peripheral venous entry to the dorsal side of the hand if necessary. However, the dorsal area of the hand is generally not recommended, especially for the application of vesicant cytotoxic drugs, where the close relationship of the tendons, muscles, blood vessels and nerves in the dorsal area of the hand is associated with a high risk of severe damage in case of extravasation. In general, forearm veins are recommended as the most suitable peripheral entry point.

Before each cytotoxic drug administration, the venous line must be checked by aspirating the blood and rinsing with at least 10-20 ml normal saline solution. The flushing volume may be even higher depending on the type of infusion set used (i.e. special closed contamination minimising infusion sets). The patient must be educated about the manifestations of extravasation and the need for early reporting of any concerns. Checks for symptoms of extravasation at regular intervals are necessary during chemotherapy application.

In case of extravasation, it is recommended to immediately stop application, avoid panic, communicate clearly and keep the patient calm, leave the venous entry in place and attempt to draw back residuals of the infusion from the affected area. Next, it is recommended to remove the peripheral cannula; however, in the case of extravasation of taxanes (paclitaxel,

docetaxel, cabazitaxel) and vinca-alkaloids (vinblastine, vincristine, vindesine, vinflunine, vinorelbine) the cannula can still be left to be eventually used for hyaluronidase administration. It is recommended not to press on the affected area or apply wet compresses (only dry hot or cold compresses should be applied depending on the type of cytotoxic drug that has be used - see below for further details). Subsequently, elevate the affected limb, mark the extravasation area and document the event. The physician must be informed to ensure other individual procedures are followed, including reporting and recording. It is not recommended to inject corticosteroids topically into the affected area.

As a next step, application of special antidotes is recommended, according to the type of cytotoxic drug extravasation, and every effort is to be made to ensure the availability of these antidotes in on-site supplies; however, the availability of individual antidotes may be limited depending on their registration and import status.

DMSO (99%) is recommended for topical application after extravasation of anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin), mitomycin C and cisplatin. In case of anthracycline extravasation, DMSO is to be applied only if dexrazoxane is not to be indicated for administration. The first dose of DMSO is optimally applied to the site of injury and an area twice the size of the affected area within 10 min after extravasation, by applying 4 drops per 10 cm^2 skin surface area, spread with sterile gauze, three times a day for at least 1 week, ensuring that the skin is not covered with a bandage or clothing (in the case of Doxorubicin-TEVA extravasation, the Czech republic SPC[13] reports application for at least 14 days, with cooling after application).

Hyaluronidase (150 U/ml) is recommended in the case of extravasation of taxanes (cabazitaxel, docetaxel, paclitaxel) and vinca-alkaloids (vinblastine, vincristine, vindesine, vinflunine, vinorelbine). The Czech republic SPC[14] does not precisely specify the procedure for its use in the case of extravasation, however, administration within 1 hour after extravasation is generally recommended. The usual dose is 1 ml (150 U) hyaluronidase per 1 ml extravasate. 150-1,500 IU of hyaluronidase should be diluted in 1 ml of water for injection, with 0.4 ml administered by the inserted cannula just prior to its removal and the remaining amount applied subcutaneously around the extravasation. Optimal use of a 25 G or 27 G needle is required, and the required volume should be administered in five doses to the extravasate. It is advisable to use a different needle for each injection (maximum daily iv doses of hyaluronidase in surgery applications are up to 4,500 U, resp. 30 ml).[14]

Dexrazoxane can be used when dealing with extravasation of anthracyclines (daunorubicin, doxorubicin, epirubicin, idarubicin). Dexrazoxane is administered intravenously into a large vein to an area distant from the extravasation site, preferably on a contralateral limb, for three days (dosing 1,000, 1,000 and 500 mg/m^2), with an initial dose no later than 6 hours after extravasation. DMSO should not be administered with dexrazoxane infusion and cold compresses should be removed 15 min before and during infusion.[1,12]

As a next step, application of dry hot or cold compresses is recommended ideally in the form of gel bags coated in a dry suitable cotton or linen fabric or paper towel to avoid direct contact between the gel bag and the skin. Dry heat is to be applied in cases of extravasation of oxaliplatin, taxanes and vinca-alkaloids: apply for the first 20-60 minutes, then 4 times a day for 15-20 minutes, for 1-2 days. Dry cold compresses should be applied in case of DMSO-treated cisplatin extravasation, anthracyclines, mitomycin C and in extravasations of all other cytotoxic drugs (except for those with recommended dry heat applications): apply for the first 20-60 minutes, then 4 times daily for 15-20 minutes, for 1-2 days.

Sun protection must be assured during dacarbazine extravasation. Follow-up controls are necessary, especially in a patient with extravasation of very risky cytotoxic drugs with potential for tissue damage or necrosis. Moreover, besides the risk, other complications (such as bleeding into the tissues, phlegmon) could occur in the case of cytopenia, especially in a haemato-oncological patient. Considering the extent of extravasation and the severity of thrombocytopenia and neutropenia on an individual basis, antibiotics with good penetration into soft tissues and thrombocyte transfusion substitution should be considered, depending on the risk of haemorrhagic manifestations (ensure platelet values of 20-50 x 10^9/l).

In case of extravasation from central venous entry into subcutaneous tissue with good accessibility (e.g. the area above or around the venous port membrane), the principles outlined above, as in the case of peripheral vein extravasation, may be used - stopping infusion and aspiration of solution by central venous catheter, etc. In case of poor localisation of the extravasate, larger volumes, and in cases of suspicion of drug accumulation in the mediastinum, pleura or subcutaneous area of the chest and neck, it is always necessary to carry out CT examination to document the affected area. Given the nature of the cytotoxic drug, an individual management plan and careful observation over at least two weeks must be ensured in collaboration with thoracic surgeons and pneumologists. Dexrazoxane is recommended for anthracycline extravasation.

4. Discussion

Ensuring reliable, safe venous access is an integral and very important part of care for chemotherapy treated patients. Due to the possible serious, long-lasting consequences of extravasation of risky vesicant and irritant cytotoxic drugs it is always necessary to follow recommended prevention and treatment procedures. In some respect, there were differences in extravasation management among individual oncology centres in our country, and some recommended procedures were considered ambiguous. We considered the revision of the procedures as important. We are pleased to have reached a consensus on chemotherapy extravasation management within twenty seven oncology and haemato-oncology centres in the Czech Republic. This written document defines several procedures and interventions that can be considered as basic and fully feasible for daily practice across all oncology centres throughout our country.

In fact, the first part of this document dealing with preventative measures, peripheral venous entry and the choice of mid-term and long-term venous access devices, corresponds very much with other available guidelines and thus it reflects a kind of mutual inter-institutional and international consensus in this issue.[1,2,5–8,10,11,15] In addition, our paperwork also provides specification for thrombocyte (platelet) values needed for safe central venous canilation with their indications, and sun protection in dacarbazine extravasation is stressed.

The most controversial recommendations that were considered were those for platin salts. There has been a great deal of controversy across literature and institutional sources concerning this issue. For example, antidote dimethylsulfoxide DMSO is mentioned in the ESMO/EONS guideline text to be used for platin salts, however this statement is not reffered to again and specifically not in the Figure 1 of the paper, and platin salts are marked within the group of drugs to be treated in the way of the "disperse and dilute" principle, which may cause confusion to the readers.[1] In the West Midlands Expert Advisory Group for Systemic Anti-Cancer Therapy guidelines (NHS England), the recommendation has been more specific, individualising platin salts drugs care: "If treatment is administered within 24 hours then a warm pack and Hyaluronidase would be the treatment of choice, however for cisplatin and carboplatin, if the injury is not treated within 24 hours a cold pack and hydrocortisone cream would then be the appropriate management (not in the case of Oxaliplatin where the cold may risk development of other symptoms)".[15] On the other hand, the Northern Ireland Cancer Network (NICaN) Regional Pharmacy Group recommends cold compresses for cisplatin and carboplatin, if an extravasated volume > 10 ml hyaluronidase is to be used, and in case of oxaliplatin warm compresses are to be used.[8] As for our recommendation, we decided, based on ESMO/EONS written text,[1] the original findings by G.Bertelli[9] and other literature sources[5,6,8,11,15] and based on the principle "localise and neutralise" (which is aplied for antracyclines a mitomycine), to specify cisplatin extravasation to be handled by DMSO and dry cold compresses, carboplatin with cold and oxaliplatin with warm dry compresses, as cold may help the development of toxicity and other symptoms in this drug.

We are aware that this is not original research in the sense of verifying the newly introduced procedure, finding new solutions and ways. However, we try to solve the problem comprehensively and we try to define the exact steps of the procedure.

Compared to other nursing and medical complications and problems, the data from original research within cytotoxic drugs exravasation has been rather limited. Even individual cytotoxic drugs have not always been considered to fall under the same strict definitions of tisue damage caused – i.e. cisplatin and oxaliplatin are variously considered irritants or vesicants).[1,5,8,11,15] It is obvious, that research and cooperation must be supported to go further in this field of nursing.

We assume that the work presented here may also be a motive for other centres to verify the availability and content of their standard procedures and compare or discuss them, as controversial or missing and inconclusive recommendations may be found. At the very least, we can share our view on this issue here.

5. Conclusion

Extravasation (paravasation) of cytotoxic chemotherapy drugs represents a very important complication in oncology nursing. Written guidelines and recommendations are important and helpful tools to have and use in daily practice, and prevention and treatment options will always be an important topic to discuss and share.

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Conflicts of Interest Disclosure

The author(s) declare that they have no competing interests.

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