Lancashire and South Cumbria Integrated Care Board

POLICY FOR THE MANAGEMENT OF EXTRAVASATION

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Policy for the management of extravasation

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INTRODUCTION

This policy intends to provide cohesive instructions for the management of extravasation in order to standardise the management of extravasation across all units where cytotoxic chemotherapy is administered within the Lancashire and South Cumbria Cancer Network.

The policy has been adapted from The Royal Marsden Manual Handbook (Mallett and Dougherty 2004) and the European Oncology Nursing Society extravasation guidelines (EONS 2007)

DEFINITION

Extravasation is the inadvertent administration of vesicant drugs into surrounding tissues, which can lead to tissue necrosis, while infiltration is the inadvertent administration of non-vesicant solutions/medications into the surrounding tissues (Weinstein 2007; RCN 2010). A vesicant is any drug, which has the potential to cause tissue damage, while irritant drugs may cause local tissue inflammation and discomfort, but do not result in necrosis and therefore tend to be dealt with more conservatively.

PREVENTION

Every effort must be made to prevent this occurring during the administration of cytotoxic drugs (Refer to policy for chemotherapy administration).

The incidence of extravasation during the administration of vesicant cytotoxic drugs is estimated to be between 0.1 and 6% (McCaffrey Boyle & Engelking 1995). Even when practitioners have many years of experience, extravasation of vesicant agents can occur and is an extremely stressful event. Early detection and treatment are crucial if the consequences of an untreated or poorly managed extravasation are to be avoided. These may include:

- Pain from necrotic areas
- Physical defect
- The cost of hospitalisation and plastic surgery
- Delay in the treatment of disease
- Psychological distress
- Litigation – nurses are now being names in malpractice allegations and extravasation injuries are an area for concern (Weinstein 2007)

However it is prevention, which remains the most effective strategy for managing this hazard to patients. This includes the following strategies:

- The use of steel winged infusion devices are associated with a greater risk of extravasation and should be discouraged. A plastic cannula should be used instead (Dougherty & Lister 2008)

- Siting over joints should be avoided as tissue damage in this area may limit joint movement in the future. It is also recommended that the anticubital fossa should never be used for the administration of vesicants (Stanley 2002; Hayden & Goodman 2005; Dougherty &Lamb 2008)

- Extra caution should be carried out in patients who at increased risk of extravasation. These include:

    a) Elderly patients
    b) Patients with fragile veins
    c) Patients who are thrombocytopenic
    d) Unconscious, sedated or confused patients
    e) Consideration should be given to patients with a pre-existing peripheral neuropathy resulting in reduced sensation to upper limbs/hands to have treatment via a centrally placed vascular access device.

- All anti-emetics should be given before any chemotherapy. Subject to any sequencing specified on the template, vesicant cytotoxics should be given before any non-vesicant/non cytotoxic drugs. The exception to this is where patients require supportive therapy e.g. pre-hydration prior to vesicant drugs, the VAD site must be monitored more frequently.

- Early recognition and prompt action comes from ensuring only skilled and knowledgeable practitioners administer vesicant drugs and/or insert the device.

Adequate information given to patients will ensure early recognition and cooperation, as patients are the first to notice pain.

SIGNS AND SYMPTOMS OF EXTRAVASATION

Extravasation should be suspected if one or more of the following symptoms have occurred:

1. The patient complains of stinging, burning pain or other acute change at the injection site. This should be distinguished from a feeling of cold, which may occur with some drugs or venospasm, which occurs with irritants.

2. Induration, swelling or leakage around the injection sight.

3. Erythema of the skin occurs around the injection site; it may not present immediately. It is important that this is distinguished from a 'flare' reaction, which is a red streak, flush or even 'blistering' associated with doxorubicin and other red coloured drugs. This occurs in about 3% of patients and does not cause any pain, although the area may feel itchy. It is caused by a venous inflammatory response to histamine release and is characterised by redness, blotchiness and may result in the formation of small weals, having a similar appearance to a nettle rash. It usually subsides within 30 to 45 minutes with or without treatment, but it responds well within a few minutes to the application of a topical steroid (Beason 1990; Wood & Gullo 1993).

4. A flashback of blood is absent – this may indicate lack of patency and incorrect position of the device. If no other signs are apparent this should not be regarded as an indication of a non-patent vein, as a vein may not bleed back for a number of reasons and extravasation may occur even in the event of good blood return. Any change in blood flow should be investigated.

5. A resistance is felt on the plunger of the syringe if drugs are given by bolus.

6. There is absence of free flow when administration is by infusion (Dougherty & Lister 2008).

MANAGEMENT OF EXTRAVASATION

The management of the extravasation of chemotherapeutic agents is controversial and there is little documented evidence of efficacy: controlled clinical trials are lacking and it is often difficult to ascertain whether an extravasation has actually occurred (Weinstein 2007, Harrold, Gould and Drey 2015). Some studies performed on animals have demonstrated both effective and ineffective treatments, but extrapolation from animals to humans is limited (Powell 1996).

Specific courses of action depend on the nature of the drug, how much has extravasated and where. Delays in recognition and treatment can increase the risk of tissue necrosis.

If extravasation is suspected, treatment should begin as soon as possible as this can reduce damage to tissues. However, extravasation may only become apparent 1-4 weeks after the administration (Ener 2004).

No matter what the nature of the drug, if extravasation is suspected the initial action remains the same. The most important thing initially is to limit the amount of drug extravasating into the surrounding tissue.

The use of an extravasation kit is recommended and should be assembled according to the particular needs of individual institutions (Appendix 1). They should be kept in all areas where staff are regularly administering vesicant drugs, so staff have immediate access to equipment (EONS 2007). The kit should be simple to avoid confusion, but comprehensive enough to meet all reasonable needs (Allwood *et al*. 1997). Instructions should be clear and easy to follow, and the use of a flow chart enables staff to follow the management procedure in easy steps.

The management of extravasation involves several stages:

Stage 1: Stop the infusion immediately and aspirate the drug.

Attempting to aspirate as much of the drug as possible, as soon as extravasation is suspected, may help to reduce the size of the area affected (Weinstein 2007). Although the likelihood of withdrawing much aspirate is small. Avoid applying direct manual pressure to the suspected extravasation site.

Stage 2: Remove the device and mark the affected area.

Stage 3: Localise and neutralise or disperse and dilute. See flow sheet for management of extravasation (appendix 2).

There are two broad approaches to limiting the damage caused by extravasation: localise and neutralise; or disperse and dilute.

Cold packs attempt to limit the spread of infusate. This was previously thought to be due to vasoconstriction. However, in animal models it appears that cold prevents spread by a mechanism other than vasoconstriction- suggested to be decreased cellular uptake of the drug at lower temperatures (EONS 2007).

Disperse and dilute strategy is appropriate for the extravasation of non- DNA binding drugs e.g.Vinca alkaloids. Warm compresses prompt vasodilation and encourage blood flow in the tissues, thereby spreading the infusate around. Hyaluronidase may be given to dilute the infusate.

In the event of an extravasation during peripheral bolus, sequential administration, the specific drug being administered at the time of extravasation reported/witnessed should be managed accordingly.

3.1 Antidotes

A number of antidotes are available, but there is a lack of scientific evidence to support many of their values, their use (including pros and cons) should be carefully considered. The antidotes currently available for treating extravasation form an important part of the “localise and neutralise” and the “disperse and dilute” strategies. For example, Savene (dexrazoxane) can help to neutralise anthracyclines; whereas hyaluronidase helps to facilitate the dilution of vinca alkaloids into the surrounding tissues. However, Savene is not currently available with the Lancashire and South Cumbria cancer Network. Provided they are used in the appropriate way and for the appropriate infusate they might help to prevent progression to ulceration, blistering and necrosis.

Antidotes used for treating extravasation include:

- Savene (dexrazoxane): The only registered antidote for anthracyclines, inhibits DNA topoisomerase ll, which is the target of anthracycline chemotherapy, blocking the enzyme so it is no longer affected by anthracyclines and damage to the cells is averted.

- Dimethylsulfoxide (DMSO): Prevents ulceration. May work by virtue of its free radical scavenging property. Administration guidelines (appendix 4).

- Hyaluronidase: Breaks down hyaluronic acid (“cement”) in connective/soft tissue, allowing for dispersion of the extravasated drug, thereby reducing the local concentration of the damaging agent and increasing its rate of absoption. Administration guidelines (appendix 5).

3.2 Steroids

Many guidelines recommend the use of subcutaneous or intradermal steroids. However, many reviews state that inflammation is not prominent in the aetiology of tissue necrosis. There is also evidence that subcutaneous or intradermal steroids may be harmful in high doses, are ineffective in certain extravasations and may increase the skin toxicity of vinca alkaloids. For this reason, this policy does not recommend the routine use of subcutaneous steroids and injectable steroids are not included in the extravasation kit. Topical hydrocortisone 1% cream is unlikely to do harm and may reduce nonspecific inflammation, except in vinca-alkaloid injuries.

Stage 4: Elevate the limb

Stage 5: Surgical advice

In the event of a large volume of drug extravasating it may be necessary to refer to a plastic surgeon for advice. Requirement for surgery is usually based on the size and location of the extravasation as well as the type of drug. Surgical removal of the tissue may be required to prevent progression of the extravasation, as well as restore function and reduce pain to the affected area. A saline flush-out procedure may also be considered to reduce damage caused by extravasation. This should only be performed by an appropriately trained practitioner and should occur within six hours of the extravasation in an attempt to reduce tissue damage (Guinta 2004).

Stage 6: Document the incident.

An extravasation must be reported and fully documented as it is an accident, and the patient will require follow-up care.

Report the incident using the local trust governance reporting system.

Stage 7: Patient information and follow up.

Patients should always be informed when an extravasation has occurred and be given an explanation of what has happened and what management has been carried out (McCaffrey Boyle & Engelking 1995). An information sheet should be given to patients with instructions of what symptoms to look out for and when to contact the hospital during the follow up period (Dougherty & Lamb 2008).

Pro-active follow up for vesicants and irritants. Follow up is individual and depends on each patient's requirements.

Anthracyclines,Vinca- alkaloids and Taxanes may show delayed symptoms and damage up to ten days following the event; therefore, extended follow up is required.

Non vesicants may not require follow up. However, patients should be advised to self-refer any problems.

(See Appendix 6 for drug groups)

Drug data information

If in any doubt, the drug data sheet should be consulted or reference made to a research trial protocol. Drugs should not be reconstituted to give solutions which are higher than the manufacturer's recommended concentration, and the method of administration should be checked, e.g. infusion, injection.

The actions listed in this procedure may not be appropriate in all these instances. Drug data sheets should always be checked, and the pharmacy departments should be consulted if the information is insufficient.

Note: The procedure detailed here has been adapted from the policy of the Royal Marsden Hospital and the extravasation guidelines (2007) for the management by nursing staff of extravasation injury, drawn up with the assistance of pharmacist and medical colleagues. It relates specifically to the management of extravasation of a drug from a peripheral cannula.

CVAD extravasation can occur as a result of a leaking or damaged catheter, fibrin sheath formation (Mayo 1998) or a port needle dislodgement (Schulmeister 1989). The consequences of an extravasation from a central venous access device are more serious and require immediate consultation with the medical team.

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Appendix 1. Extravasation Kit

Management of extravasation involving a peripheral cannula.

To assist the nurse, an extravasation kit should be assembled and should be readily available in each ward/unit. It contains:

1. **Instant cold pack × 1/instant hot pack × 1 (or reusable packs which can be frozen or heated as required)**
2. **1x Hyaluronidase injection 1500IU**
3. **1x Dimenthylsulfoxide solution (DMSO) 95%**
4. **Hydrocortisone cream 1% 15g tube × 1**
5. **2ml syringes × 1**
6. **25g needles × 2**
7. **Alcohol swabs**
8. **Indelible Pen for marking the affected area**
9. **Copy of extravasation management procedure**
10. **Patient information leaflet**

Appendix 2. Flow chart for the management of extravasation

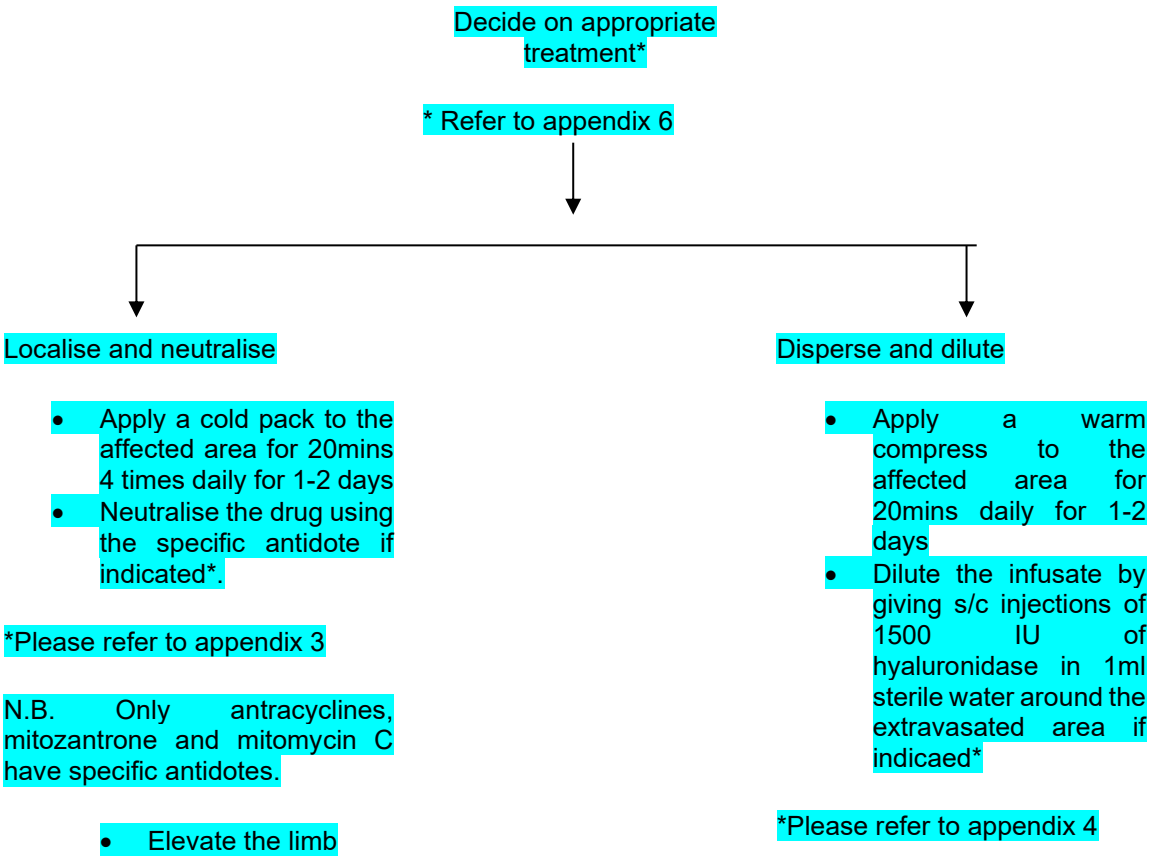
Step 1: Stop the infusion and disconnect from vascular access device. Do not remove.

Step 2: Aspirate as much from the vascular access device as possible.

Step 3:Remove the peripheral cannula with minimal pressure to the surrounding tissue. Extravasation of cyctotoxics administered centrally should be referred to a consultant.

Step 4: Mark the affected area with an indelible pen.

Step 5:



Step 6: Inform medical staff. Urgent plastics review should be sought for extravasation of vesicant drugs.

Step 7: Provide analgesia as required

Step 8: Measure injury at the widest point and document the procedure.

Step 9: Provide patient information leaflet on extravasation and arrange follow up as appropriate.

Appendix 3. Administering dimethylsulfoxide (DMSO)

Dimethylsulfoxide (DMSO 95%) is an option for the treatment of extravasation with doxorubicin, idarubicin, epirubicin, actinomycin D, mitomycin C and mitozantrone.

Steps for administration:

1. Follow steps for localisation and neutralisation
2. Put gloves on
3. Apply thin layer of DMSO topically to the marked area
4. Allow it to dry
5. Apply a non-occlusive dressing
6. Check for erythema caused by DMSO
7. Repeat every 8 hrs for up to 5-7 days if required.

Please refer to DMSO 95% prescribing information for a full list of contraindications, precautions and warnings.

Appendix 4. Administering hyaluronidase

Steps for administration:

1. Follow steps for dispersion and dilution of extravasation

2. Administration of hyaluronidase should begin within an hour of extravasation for the best results

3. Dilute 1500 IU of hyaluronidase in 1ml of 0.9% sodium chloride

4. Inject 0.1-0.2ml subcutaneously at points of the compass around the periphery of the extravasation.

Appendix 5. Classification of drugs

Ref:

Neutrals: Group 1	Inflammitants: Group 2	Irritants: Group 3	Exfoliants: Group 4	Vesicants: Group 5
Aldesleukin (IL-2)	Etoposide Phosphate	Bortezomib	Aclarubicin	Amsacrine
Asparaginase	Fluorouracil	Cabazitaxel	Cabazitaxel	Bendamustine
Avelumab	Methotrexate	Carboplatin	Cisplatin	Carmustine
Azacitidine	Raltitrexed	Etoposide	Daunorubicin Liposomal	Dacarbazine
Beta-Interferons		Irinotecan	Docetaxel	Dactinomycin
Bevacizumab		Teniposide	Doxorubicin Liposomal	Daunorubicin
Bleomycin		Trastuzumab-Emtansine (Kadcyla)	Floxuridine	Doxorubicin
Carfilzomib		Zoledronic acid	Mitoxantrone	Epirubicin
Cetuximab		Sacituzumab Govitecan	Oxaliplatin	Idarubicin
Cladribine		Trastuzumab Deruxtecan	Topotecan	Mitomycin
Cyclophosphamide				Mustine
Cytarabine				Nab-Paclitaxel (Abraxane)
Daratumumab				Paclitaxel
Durvalumab				Streptozocin
Edroclomab				Treosulfan
Eribulin				Vinblastine
Fludarabine				Vincristine
Fluvestrant				Vindesine
Gemcitabine				Vinorelbine
Gemtuzumab				
Ifosfamide				
Ipilimumab				
Melphalan				
Nivolumab				
Pentostatin				
Polatuzumab Vedotin				
Rituximab				
Thiotepa				
Trastuzumab				
Obinutuzumab				
Dostarlimab				
Cemiplimab				

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http://www.bccancer.bc.ca/drug-database-site/Documents/Extravasation%20Hazard%20Table.pdf

Appendix 6: individual drug management

DRUG	DISPERSE AND DILUTE	LOCALISE (AND NEUTRALISE IF INDICATED)	ADDITIONAL INFORMATION
Alemtuzumab			No specific action
Amsacrine		X	Apply topical DMSO
Arsenic		X	
Asparaginase	X		Infiltrate with hyaluronidase
Bendamustine		X	
Bevacisumab		X	
Bleomycin			No specific action
Brentuximab			No specific action
Bortezomib			No specific action
Carboplatin		X	
Cabazitaxel	X		Infiltrate with hyaluronidase
Carmustine		X	
Cetuximab			No specific action
Cemiplimab			No specific action
Cisplatin		X	
Cladribine			No specific action
Cyclophosphamide			No specific action
Cytarabine			No specific action
Dacarbazine		X	
Dactinomycin		X	Apply topical DMSO
Daratumumab			No specific action
Daunorubicin		X	Apply topical DMSO
Docetaxel	X		Infiltrate with hyaluronidase
Doxorubicin		X	Apply topical DMSO
Dostarlimab			No specific action

DRUG	DISPERE AND DILUTE	LOCALISE (AND NEUTRALISE IF INDICATED)	ADDITIONAL INFORMATION
Epirubicin		X	Apply topical DMSO
Eribulin		X	
Etoposide		X	
Fludarabine		X	
Fluorouracil		X	
Gemcitabine		X	
Idarubicin		X	Apply topical DMSO
Ipilimumab			No specific action
Ifosfamide		X	
Irinotecan		X	
Melphalan		X	
Methotrexate		X	
Mitomycin C		X	Apply topical DMSO
Mitozantrone		X	Apply topical DMSO
Nivolumab			No specific action
Obinutuzumab			No specific action
Oxaliplatin	X		Infiltrate with hyaluronidase
Paclitaxel	X		Infiltrate with hyaluronidase
Panitumumab			No specific action
Pentostatin	X		Infiltrate with hyaluronidase
Pemetrexed		X	
Pembrolizumab			No specific action
Pertuzimab			No specific action
Pixantrone			Non vesicant
Ralitrexed		X	
Rituximab			No specific action
Sacituzumab Govitecan		X	

Streptozocin		**X**	
Temsirolimus			**No specific action**
Topotecan		**X**	
Trabectedin		**X**	
Traztuzumab			**No specific action**
Trastuzumab Deruxtecan		**X**	
Trastuzumab Emtansime		**X**	
Treosulphan		**X**	
Vinblastine	**X**		**Infiltrate with hyaluronidase**
Vincristine	**X**		**Infiltrate with hyaluronidase**
Vindesine	**X**		**Infiltrate with hyaluronidase**
Vinflunine	**X**		**Infiltrate with hyaluronidase**
Vinorelbine	**X**		**Infiltrate with hyaluronidase**