NCCP Guidance: Prevention and Management of Extravasation of Systemic Anti-Cancer Therapy (SACT)

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1 Glossary

Cannula	A hollow plastic flexible tube containing an introducer needle (stylet) that may be inserted into a blood vessel.
Central venous access device (CVAD)	A catheter that is threaded into the central vasculature, the tip of which is placed in the lower one third of the superior vena cava, inferior vena cava or the right atrium. CVADs can be used for the delivery of intravenous (IV) medications, IV fluids, parenteral nutrition solutions, blood and blood products.
Cytotoxic[1]	A therapeutic agent intended for, but not limited to, the treatment of cancer. Cytotoxic drugs are hazardous drugs that exhibit one or more of the following characteristics in humans or animals: carcinogenicity, mutagenicity (genotoxicity), teratogenicity, reproductive or developmental toxicity, organ toxicity at low doses.
Disperse and dilute	A management strategy for extravasation of specific drugs which involves the application of a warm compress to the affected site. This causes vasodilation which increases drug distribution and aids in sides in the dispersal of the drug from the injury site. Agents which increase resorption such as hyaluronidase may be used as per local policy.
Erythema	Redness of the skin caused by dilatation and congestion of the capillaries, often a sign of inflammation or infection.
Extravasation	Escape / accidental leakage of a liquid from a vessel into the surrounding tissue or subcutaneous spaces during an IV administration In cancer treatment, it refers to the leakage of SACT during administration. Extravasation may be painful or non-painful.

[1] HSE Guideline on the Safe Handling of Cytotoxic Drugs 2022. Available at: https://healthservice.hse.ie/filelibrary/staff/hse-guideline-on-the-safe-handling-and-use-of-cytotox-drugs.pdf

Flare reaction	Local, non-painful, possibly allergic reaction often accompanied by reddening along the vein. Distinguishable from extravasation by the absence of pain and swelling and the presence of blood return.
Infiltration	Unintentional instillation or leakage of a non-vesicant medication or fluid out of a blood vessel into surrounding tissue.
Irritant	Drug that causes burning sensation, pain, phlebitis, tightness with or without inflammation at extravasated injection site or along the vein.
Intravenous cannula (IVC)	A small plastic tube that passes through the skin into a vein. It is often called an IV line or a drip. A needle is used to put the tube in through the skin.
Localise and neutralise	A management strategy for extravasation of specific drugs which involves the application of a cold compress to the affected site. This causes vasoconstriction which minimises the spread of drug from the initial injury site and decreases cellular uptake of the drug. Specific neutralising agents may be used as per local policy.
Neutral (non-irritant)	Drug that does not cause local irritation when extravasated.
Phlebitis	Local inflammation of the vein due to endothelium with or without vasospasm.
Peripherally inserted central catheter (PICC)	A thin, flexible tube that is inserted into a vein in the upper arm and guided (threaded) into a large vein above the right side of the heart called the superior vena cava. This is a type of CVAD (see above).
Systemic Anti-Cancer Therapy (SACT)	SACT involves systemic treatment for cancer; involving parenteral and oral anti-cancer therapies, including but not limited to cytotoxic chemotherapy, monoclonal antibodies such as targeted therapies and immunotherapies
Vesicant	Drug or substance that has the ability to cause blistering, local or extensive necrosis with or without tissue ulceration. These are classified into DNA binding and non-DNA binding vesicants.
Vesicant - DNA binding	Absorbed locally and enters the cells, binds to DNA and precipitates the death of the cell. DNA binding vesicants include anthracyclines and alkylating agents.
Vesicant - non-DNA binding	Initiates cell death by mechanisms other than binding DNA. Non-DNA binding binding drugs include taxanes and vinca alkaloids.
Vessel Irritation	Aching and tightness which occurs along the vein. Applying warmth to dilate the vein can relieve this. Blood return is usually intact although erythema or redness may be present.

2 Introduction

Systemic Anti-Cancer Therapy (SACT) is one of the main cancer treatment options together with surgery and radiation. Drugs used in SACT, particularly cytotoxic chemotherapy, can be extremely irritating and cause damage if they extravasate or infiltrate into surrounding tissues during intravenous (IV) administration. Extravasation refers to the inadvertent infiltration of any liquid (fluid or drug) from a vein into the subcutaneous or subdermal tissues during IV administration (1). Depending on the type, extravasation can result in damage to the tissues and cause pain, erythema, swelling and blistering. If left undiagnosed or inappropriately treated, this can lead to necrosis, secondary infection and functional loss of the tissue or possible permanent damage to the limb involved (2).

The NCCP Oncology Medication Safety Review Report (2014) (3) recommended that each hospital should have a written policy governing the prevention, recognition and treatment of extravasation[2]. Most hospitals delivering SACT services develop and maintain local extravasation policies. To support these, the NCCP have developed the following:

- NCCP Background Document on Extravasation Classification (2017)[3] (4).
- NCCP Standardised Patient Assessment Form for the assessment of suspected or diagnosed extravasation injury[4].

This guidance document details the key considerations in the prevention, recognition and management of extravasation of SACT for use in hospitals delivering SACT services, as informed by published literature and international practice. It is intended to support hospitals, acknowledging that individual circumstances will arise; clinicians should exercise their own judgement as to the most appropriate approach. The guidance should be incorporated into each hospital's local extravasation policies as applicable to the type of SACT service provided.

[2] NCCP Oncology Medication Safety Review Report (2014); Recommendation 62

[3] NCCP Background Document Extravasation Classification of SACT. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/classification.pdf

[4] NCCP Patient Assessment Form for Extravasation. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/extravasation.html

3 Scope

This document provides guidance on the management of extravasation for staff[5] involved in the administration of SACT to patients with cancer.

The management of flare reactions and vessel irritation are beyond the scope of this document and should be treated according to local policy.The extravasation of drugs not used in the treatment of cancer is outside the scope of this document.

Where there is any doubt regarding the cause of an injury, it is recommended that the injury should be treated as an extravasation.

4 Methodology

This guidance document is informed by published literature as well as local and international practice. This document was developed and agreed by the NCCP in consultation with the NCCP Parenteral SACT Resilience Group and with input from NCCP Nursing.

5 Prevention of Extravasation

5.1 Extravasation Classification of SACT

The NCCP Extravasation Classification Document (4)[6] classifies parenteral SACT into four different types, depending on their ability to cause local damage after extravasation:

- Vesicants DNA Binding
- Vesicants Non DNA Binding
- Irritants
- Neutrals (Non vesicants)

[5] Staff involved in SACT administration should be trained in the recognition, management and treatment of extravasation.

[6] NCCP Background Document Extravasation Classification of SACT. Available at:

https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/classification.pdf

5.2 Risk Factors for Extravasation

Risk factors for consideration can be classed into four categories – patient-related, medication-related, infusion-related and device-related. The following list is not exhaustive.

While the SACT drug itself can cause injury when extravasated, the properties of the drug solution may also contribute to the potential for injury. Infusates with pH values that are very low or very high and infusions of hypo- or hyperosmolar agents can be harmful to tissues and can lead to tissue damage (5, 6).

Table 1: Extravasation risk factors for consideration

Risk factor	Risk factor detail
Patient-related (7)	• age • vein integrity and availability • co-morbidities • limb movement causing displacement of cannula • circulation or coagulation disorders / abnormalities, cognitive ability, dermatological conditions
Medication-related	• vesicant potential (refer to NCCP Extravasation Classification Document[7]) • multiple vesicants within a treatment regimen • drug concentration and chemical properties • drug volume
Infusion-related	• flow pressure • infusion duration
Device-related	• choice of cannulation e.g. cannula type and size, needle type, central or peripheral • cannulation site and number of cannulation attempts • choice of dressing e.g. to ensure cannula or gripper fixed to skin securely • location and patency of port • occurrence of backflow[8] • CVAD damage, separation or displacement

[7] NCCP Background Document Extravasation Classification of SACT. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/classification.pdf

[8] Blood return must be confirmed prior to use of CVAD

5.3 Extravasation Prevention

The following measures should be considered to prevent extravasation and incorporated into local policies as appropriate.

Table 2: Measures to consider in the prevention of extravasation

Measure	Details of measure
Staff training and competency	• Appropriate training of staff involved in SACT administration. • The NCCP have made available the NCCP National SACT Competency Programme for Nurses Working in Cancer Care (8).

Cannulation and vascular access	• For peripheral IV sites, ideally site new cannula noting the older the site, the less the integrity of the vein
	• Consider cannula size, type[9] and location including the avoidance of;
	  ○ insertion of a cannula over joints, the inner wrist, lower extremities, antecubital fossa or where lymphoedema is present
	  ○ veins next to nerves, tendons or arteries
	  ○ small and fragile veins
	  ○ multiple punctures
	  ○ administering cytotoxic drugs below a previous venepuncture site
	• Vein selection; consider:
	  ○ Recent venepuncture
	  ○ Post mastectomy patients e.g. consider use of contra-lateral arm

SACT administration	Consider: • Vesicant potential of SACT • Order of administration of SACT • PICC / central line for certain SACT e.g. those classified as vesicants, multiple vesicants • Use of infusion pump; may not be suitable for some SACT e.g. vesicants • Patency of line / port
Patients	• Education

[9] The use of steel-winged infusion devices are associated with a greater risk of extravasation and should be discouraged.

6 Management of Extravasation

Extravasation management should consider the drug that has caused the extravasation, the classification of the drug and an assessment of the extravasation site.

Where it is suspected that an extravasation has occurred, it should be managed as an emergency and referred immediately to the treating medical team. Early detection and prompt action is key to the successful management of an infiltration / extravasation. Early initiation of treatment is critical, regardless of SACT drug involved.

Clinical judgement is involved when treating an infiltration / extravasation and each injury should be assessed and managed on an individual patient basis.

The NCCP have made available a standardised Patient Assessment form[10] for Extravasation for use by hospitals.

6.1 Extravasation Kit

All areas of the hospital in which IV cytotoxic drugs are administered should have facilities available for the immediate treatment of cytotoxic extravasations, as recommended in the NCCP Oncology Medication Safety Review Report 2014 (3).

Facilities should include the availability of an 'Extravasation Kit'. Each hospital should determine locally what is to be included; a suggested minimum list of contents (not exhaustive) can be found in Appendix 1 and will need to be amended according to local practice.

The contents of the Extravasation Kit should be regularly checked to ensure that items have not expired.

6.2 Recognition of an Extravasation / Infiltration

An infiltration / extravasation should be suspected if one or more of the following signs and / or symptoms are present:

- Pain / tingling
- Swelling / redness
- Lack of blood return from cannula / CVAD[11].
- Syringe resistance when administering a bolus medication or a change in the rate / flow of infusion

[10] NCCP Patient Assessment Form for Extravasation. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/extravasation.html

[11] If found in isolation, this is not always a sign of infiltration / extravasation.

To note that extravasation from a CVAD may be more difficult to detect and although less likely to occur than from a peripheral cannula, can be more severe.

Common signs of central catheter infiltration / extravasation:

- pain in shoulder / neck
- pain in chest wall
- leakage from catheter exit site / along subcutaneous canal or other change in the rate / flow of infusion
- swelling of chest wall

If there is any doubt regarding the cause of an injury, the injury should be treated as an extravasation.

6.3 Steps to be considered in the Management of Extravasation

Each hospital's local extravasation policy should detail the steps to be followed in the management of extravasation and should consider the following:

Table 3: Steps to be considered in the management of an extravasation

Steps to be considered in the management of an extravasation (see Appendix 4 and 5)

• Discontinuation of the infusion and management of the cannula
• Notifying the medical team (+/- surgical team as appropriate e.g. CVAD)
• Informing and educating the patient
• Use of the extravasation kit, including any treatment in line with locally agreed steps
  ○ Consider class of SACT. In general:
  ▪ Vesicant (DNA binding) – localise and neutralise: use of cold compress
  ▪ Vesicant (Non DNA binding) – dilute and disperse: use of warm compress
  ▪ Irritant – use of cold compress may be considered (with the exception of etoposide and oxaliplatin as per Appendix 3).
  ▪ Non – vesicant / neutral (usually no compress required. Monitor).
  ○ Use of antidotes may be considered
• Ensure completion of documentation. Please refer to the **NCCP Patient Assessment form for Extravasation**[12] for more details
• Follow up care
• Ensuring replacement of extravasation kit

[12] https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/extravasation.html

Please refer to the following Appendices for additional information

Appendix 2 and Appendix 3 outline more detailed information in relation to the use of warm / cold compress and management of extravasated SACT drugs.

Appendix 4 and Appendix 5 outline summary procedures for the management of peripheral and central line extravasation.

6.4 Antidotes used in the management of extravasation

Evidence in the area of extravasation management for SACT is limited (9). Recommendations regarding treatment of SACT extravasation are based on limited evidence and are often conflicting (10).

Each hospital should have a written SOP detailing the list of antidotes available where SACT is administered (see Appendix 3 which details a Table of SACT drugs and suggested antidotes that may be considered for inclusion in the local extravasation policy). Hospitals should consider their local practice including the type of SACT administered in their hospital to determine if a stock of these items is required. Please refer to Appendix 2 and Appendix 3 for more detailed information.

7 References

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Appendix 1. Suggested Extravasation Kit Contents

Inclusion of suggested contents in this guidance does not denote NCCP endorsement; consideration should be given locally to the contents of the Extravasation Kit **(Refer to local policy).**

Category	Suggested items
Antidotes	**Any antidotes agreed locally for consideration**
Consumables	3ml Luer Syringes 5ml Luer syringes 10ml Luer syringes 19 gauge needles (for drawing up) 25 gauge needles (for injection) Sodium chloride 0.9% mini-plasco ampoules Water for injection mini-plasco ampoules 10ml Nitrile gloves tested for use with hazardous drugs Clinell® Alcoholic 2% Chlorhexidine wipes
Documentation	Printed up to date copy of extravasation guidance and local policy
Other equipment	Black indelible ink marker Instant cold pack / instant hot pack. Cold packs should be kept in the fridge and labelled “For Extravasation only” Sterile gauze dressing and tape Sling
Symptom control	Anthisan® cream Chlorphenamine 4mg tablets or IV injection (10mg/ml) ampoules Hyaluronidase injection 1500 unit ampoule Hydrocortisone 1% cream 1 x 15g tube

Appendix 2. Application of cold and warm compresses

For each SACT drug, there is a recommendation to either apply heat or cold to the extravasation site (6, 7, 11).

The application of warm or cold compresses should consider the drug extravasated and each hospital's policy should outline the local processes

Type of Compress	**Mechanism of action**	**Directions for use**	**Use with the following drugs**
Cold	• causes vasoconstriction • minimises the spread of drug from the initial injury • allows time for local vascular and lymphatic systems to disperse the agent • reduces local inflammation and pain and decreases cellular uptake of the drug	Apply to the affected site four to five times a day for 15-20 minutes over the next 24 to 48 hours after the extravasation	Irritants and Vesicants (DNA-binding) (Except etoposide and oxaliplatin and vasopressors)
Warm	• causes vasodilation • increases drug distribution and absorption • aides in the dispersal of the drug from the injury site • decreases the swelling and discomfort and may reduce irritation to the tissue	Apply to the injection site four to five times a day for 15-20 minutes over the next 24 to 48 hours after the extravasation	Vesicant drugs (non-DNA binding) and specific drugs including vinca alkaloids, etoposide, vasopressors, and oxaliplatin

Appendix 3. Management of extravasated drugs

The NCCP Extravasation Classification Document (4)[13] classifies parenteral SACT into four different types, depending on their ability to cause local damage after extravasation. Local extravasation policies should consider this and align where possible, considering local practice.

The following **sample** table categorises SACT drugs according to their extravasation potential and includes suggested compress and antidotes (adapted from EviQ[14]). Hospitals should consider including a similar table in their local extravasation policy and ensure that this is kept up to date.

Extravasated Drug	Suggested Compress	Suggested Antidote
Vinca Alkaloids VinBLAStine vinCRIStine vindesine vinflunine vinorelbine	Warm	• Hyaluronidase
Anthracyclines DAUNOrubicin DOXOrubicin EpiRUBicin IDArubicin	Cold	• Dexrazoxane • DMSO 99% or 50% (For PERIPHERAL-LINE extravasations if dexrazoxane is unavailable or cannot be started within 6 hours)
Antibiotics MitoMYcin C DACTINomycin	Cold	• DMSO 99% or 50%
Liposomal anthracyclines Liposomal DAUNOrubicin Liposomal DOXOrubicin	Cold	• No recommended antidote
Taxanes PACLitaxel[15] PACLitaxel NAB	Warm	• Hyaluronidase: – There have been some clinical reports of positive outcomes with using hyaluronidase as an antidote for PACLitaxel extravasations (11).

[13] NCCP Background Document Extravasation Classification of SACT. Available at:

https://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/sactguidance/classification.pdf

[14] https://www.eviq.org.au/clinical-resources/extravasation/1002-quicklink-summary-table-treatments-for-extr

[15] For PACLitaxel extravasations, some guidelines suggest the application of ice (6), although EONS/ESMO guidelines suggest application of heat in this setting because the taxanes, similar to the vinca alkaloids, are non-DNA-binding agents and the general strategy for these types of extravasations is to dilute and diffuse.

Extravasated Drug		Suggested Compress	Suggested Antidote
			– If hyaluronidase is administered for a PACLitaxel extravasation, no compress is recommended.
Monoclonal antibodies		Not indicated	• No recommended antidote
Alemtuzumab Atezolizumab Avelumab Bevacizumab Blinatumomab Brentuximab vedotin Carfilzomib Cetuximab Daratumumab Dinutuximab Durvalumab Ipilimumab	Nivolumab Obinutuzumab Ofatumumab Panitumumab Pembrolizumab Pertuzumab Polatuzumab vedotin Ramucirumab riTUXimab Siltuximab Trastuzumab		
Other agents (vesicant DNA binding)		Cold	• DMSO 99% or 50%
Amsacrine			
Bendamustine[16] Carmustine Trabectedin		Cold	• No recommended antidote
Mechlorethamine		Cold	• Sodium thiosulfate[17]
Other agents (irritants)		Cold	• No recommended antidote
Arsenic trioxide Busulfan CARBOplatin CISplatin Dacarbazine DOCEtaxel[16] Fluorouracil Gemtuzumab ozogamicin Ifosfamide	Irinotecan Melphalan Mitoxantrone[16] Streptozocin Temozolomide Teniposide Topotecan Trastuzumab emtasine (Kadcyla®)		
Bortezomib Azacitidine		Not indicated	• No recommended antidote

[16] Single case reports describe both irritant and vesicant properties (1).

[17] Due to lack of evidence, sodium thiosulfate is recommended only for extravasation of mechlorethamine (6).

<table>
<tr><th colspan="2">Extravasated Drug</th><th>Suggested Compress</th><th>Suggested Antidote</th></tr>
<tr><td colspan="2">Etoposide</td><td>Warm</td><td></td></tr>
<tr><td colspan="2">Oxaliplatin[16]</td><td>Warm</td><td>• No recommended antidote
• Oral glucocorticoids may be of benefit in patients who have extravasated large amounts of oxaliplatin.</td></tr>
<tr><td colspan="2">Other agents (non-irritants, neutral)</td><td rowspan="2">Not indicated</td><td rowspan="2">• No recommended antidote</td></tr>
<tr><td>Aflibercept
Aldesleukin
Amifostine
Asparaginase[18]
Bleomycin
Cladribine
Clofarabine
Cyclophosphamide
Cytarabine
Decitabine
Eribulin mesilate
Fludarabine
Gemcitabine</td><td>Inotuzumab ozogamicin
Interferons
Methotrexate
Mifamurtide
Nelarabine
Pegasparaginase
Pemetrexed
Pentostatin
Pixantrone
Ralitrexed
Temsirolimus
Thiotepa</td></tr>
</table>

[18] Retest for asparaginase hypersensitivity before giving further doses.

Appendix 4. Summary of procedure for management of peripheral line extravasation (adapted from ESMO) (1)

Step 1
Stop and disconnect infusion. Inform the patient. Leave the needle in place.

Step 2
Identify extravasated agent.

Step 3
Leaving the cannula in place, try to gently aspirate as much extravasated solution as possible. Record volume removed in patient records. Avoid manual pressure over the extravasated area. Remove cannula.

Step 4
Mark with a pen an outline of the extravasated area.

Step 5
Notify physician. Start specific* measures as soon as possible (i.e. any antidotes as per local agreement and policy).

Vesicant or irritant

Non vesicant

Localise and neutralise
Agents:
Anthracyclines
Antibiotics (mitoMYcin C, DACTINomycin)

Disperse and dilute
Agents:
Vinca alkaloids
Taxanes

Local dry cold compresses

Step 5A: Localise
Apply dry cold compresses for 20 minutes four times daily for 1-2 days. Avoid alcohol compresses.

Step 5A: Disperse
Apply dry warm compresses for 20 minutes four times daily for 1-2 days.

Step 5B: Neutralise
Use specific antidotes
Anthracyclines:
Dexrazoxane
Topical DMSO
MitoMYcin C:
Topical DMSO

Step 5B: Dilute
Administer agents increasing resorption
Vinca alkaloids and taxanes:
Hyaluronidase

Step 6: Elevate the limb. Administer analgesia if necessary.

Appendix 5. Summary of procedure for management of central line extravasation (adapted from ESMO) (1)

Step 1
Stop and disconnect infusion. Inform the patient. Do not remove the cannula.

Step 2
Identify extravasated agent.

Step 3
Leaving the central venous access device in place, try to gently aspirate through the cannula as much extravasated solution as possible. Record volume removed in patient records. Avoid pressure in the surrounding area. Start non-specific measures if applicable.

Step 4
Specific measures. If drug extravasated is an anthracycline, consider early administration of IV dexrazoxane.

Step 5
Identify extravasated area. Urgent chest X-ray or thoracic CT. Immediate consultation with surgeon.

Pleura
Step 6: Consider urgent thoracocentesis and thoracic tube

Mediastinum
Step 6: Consider urgent thoracoscopy or thoracotomy

Subcutaneous
Step 6: Consider surgical drainage of cumulated solution

Fluid therapy
Analgesia
Consider antibiotic and oxygen therapy

Progressive resolution
Outpatient management

Progressive withdrawal of analgesia

Remove central venous device

Consider new insertion of a contralateral central venous device or peripheral cannula for next infusions

No resolution
Perform CT

Consider other surgical procedures