Haemorrhagic cystitis management in adult cancer guideline

Category:	Guideline
Summary:	This guideline describes the approach to diagnosis and management of non-infectious haemorrhagic cystitis (HC) in adult cancer patients, particularly when receiving systemic anti-cancer treatment (SACT) with heightened risk of causing HC.
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Distribution:	Oncology Directorate (includes both Oncology & Haematology specialties), all medical, nursing and pharmacy staff in contact with and caring for patients with a diagnosis of cancer or receiving SACT.
Related documents:	NSSG Haematology and TVCA Oncology SACT protocols
Author(s):	Dr Saba Imitaz, Consultant Oncologist Donna Constantine, Advanced Cancer Pharmacist Dr Rob Watson, Specialist Oncology Registrar
Further information:	Refer to individual SACT treatment protocol on TVCA / NSSG
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This document replaces:	New document

This document is uncontrolled once printed.

It is the responsibility of all users to this document to ensure that the correct and most current version is being used.

This document contains many hyperlinks to other related documents. All users must check these documents are in date and have been ratified appropriately prior to use.

Document history

Date of revision	Version number	Author	Reason for review or update

Consultation schedule

Who? Individuals or Committees	Rationale and/or Method of Involvement
Ambulatory Care Nurses	Guideline distribution for comment prior to publication as frequent users of relevant SACT regimens
Sarcoma / Lymphoma teams	Guideline distribution for comment prior to publication as frequent users of relevant SACT regimens

Endorsement

Endorsee Job Title
Lead Cancer Pharmacist
Lead SACT Clinician
Lead SACT Nurse

Contents

Who should read this document?

This document should be read by clinical staff routinely involved in the treatment and care of cancer patients receiving systemic anti-cancer treatment (SACT).

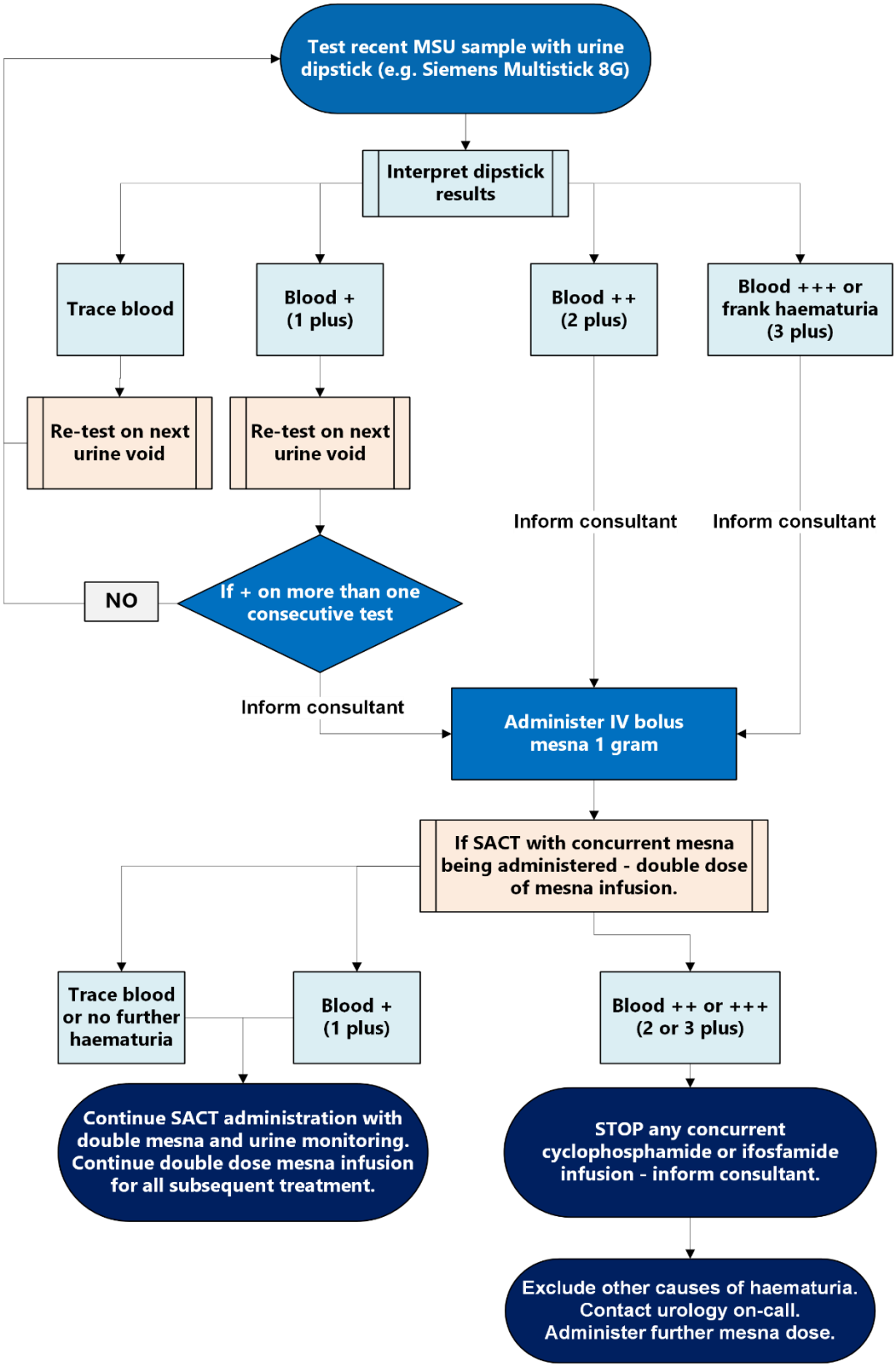
These guidelines are also relevant to staff groups using cyclophosphamide for non-cancer indications such as vasculitis in intensive care unit (ICU), rheumatology or in renal medicine.

Key standards / messages

- Mesna must be prescribed alongside any known bladder-irritant SACT (e.g. cyclophosphamide doses >1 g/m^2, ifosfamide).
- All fluid input and output volumes must be correctly recorded on EPR for calculation of fluid balance.
- Fluid balance is recommended alongside high-dose methotrexate infusions and continuous ifosfamide infusions.
- Patients receiving bladder irritant high-dose SACT should be monitored for evidence of haematuria via urine dip both before and during treatment.
- Urine samples must be dipped immediately following bladder void and significant results escalated to the medical team promptly.
- Evidence of haematuria on dipstick must be responded to quickly in line with the flowchart in the Quick Reference flowchart and management guidance within document.

Quick reference - Flow chart for managing haematuria on urine dip

Utilise in conjunction with management advice below.



1 Background

Haemorrhagic cystitis (HC) is an inflammatory process characterised by diffuse bladder mucosal inflammation resulting in haemorrhage. Whereas this may be driven by an infective process (e.g. BK virus), non-infectious HC results from **direct toxicity of antineoplastic drugs to the urothelium, or toxicity from pelvic radiotherapy** when the bladder is within the treatment field.

RT to the pelvic area can result in acute and chronic injuries to the bladder including radiation-induced HC. Radiation-induced HC is defined as sudden or gradually worsening diffuse vesical bleeding. Early-onset RT injuries to the bladder are generally associated with damage to the rapidly dividing cells of the bladder mucosa which can cause inflammation and tissue oedema (swelling). Late-onset bladder injury resulting in HC follows the progressive obliteration of the small blood vessels of the bladder mucosa (obliterative endarteritis) with consequent development of hypoxia and tissue damage resulting in development of haematuria.

HC is most frequently associated with the oxazaphosphorine alkylating agents ifosfamide and cyclophosphamide doses more than 1g per m^2. During use of ifosfamide and cyclophosphamide, the liver metabolises these agents to acrolein which is excreted by the kidneys. Prolonged contact of acrolein with the bladder mucosa causes a complex inflammatory response (pyroptotic reaction) in the bladder urothelium. Morphologic and histologic evidence demonstrates this response as swelling, bleeding, and ulceration of the bladder mucosa which leads to HC.

The incidence of HC is increased when higher, or larger, cumulative doses of ifosfamide and cyclophosphamide are used. Microscopic haematuria occurs in approximately 5 to 18 % cases, however when ifosfamide is administered with the uroprotectant mesna gross haematuria is uncommon (less than 5% of cases).

Severe cases of HC may require aggressive treatment measures and can be associated with significant morbidity, prolonged hospitalisation, and occasional mortality.

2 Key updates

Not applicable – new guideline.

3 Aim

This guideline aims to improve the recognition and management of non-infectious haemorrhagic cystitis (HC), particularly that caused by SACT.

4 Aetiology

HC can be caused by a range of medicines or agents as below in Table 1.

Table 1 – Examples of medicines or agents implicated in haemorrhagic cystitis (HC)

Medicine or agent	Risk
Ifosfamide	Very common: More than 10% patients
Cyclophosphamide	Common: 1 – 10% patients
Busulfan	Very common: More than 10% patients – this incidence rate may be confounded by post-transplant viral infection.
Thiotepa	Very common: More than 10% patients – this incidence rate may be confounded by post-transplant viral infection.

Allopurinol	Very rare: <0.01%
Penicillins	Rare: <1%
Radiation therapy to the pelvic area	Affected by total dose of radiation, volume irradiated, fractionation schedule and technique
Dyes, pesticides	Variable dependent on agent / degree of exposure

HC can be caused by infections resulting from a range of microbial, viral, fungal or parasitic causes. Infectious causes are common and often experienced by immunosuppressed patient populations.

- **Viral:** BK virus, herpes virus, JC virus, adenovirus, cytomegalovirus (CMV) – particularly in the allogeneic transplant population.
- **Bacterial:** E.Coli, Klebsiella, Staph saprophyticus, Proteus mirabilis
- **Fungal:** Candida albicans, cryptococcus neoformans, aspergillus fumigatus, torulopsis glabrata
- **Parasitic:** Schistosomiasis haematobium

Individual patient factors also increase risk:

- Previous urothelial toxicity or pre-existing bladder pathology
- Prolonged or high-dose treatment exposure
- Poor hydration
- Concomitant use of other urotoxic drugs
- Blood and marrow transplant (BMT) donor-recipient gender mismatches (early onset) or bone marrow as a source of stem cells (late onset)
- Systemic disease, i.e. amyloidosis

5 Clinical presentation

The clinical presentation of HC is variable, ranging from mild haematuria (i.e. subclinical and only detected on urine dip) to gross haematuria with clots and life-threatening persistent haemorrhage.

Patients may experience lower urinary tract symptoms. There may be suprapubic discomfort, flank, or back pain if an upper urinary tract or bladder outlet obstruction occur secondary to blood clots obstructing the flow of urine (clot retention).

Onset can occur during or immediately following SACT treatment, typically bleeding develops 24 to 48 hours after a single dose and may last four to five days.

In rare cases, symptoms may be delayed for months to years following treatment.

6 Signs and symptoms

- Haematuria, micro- to macroscopic, with or without blood clots
- Dysuria
- Urinary frequency, urgency or incontinence
- Nocturia
- Suprapubic/vague abdominal discomfort and/or pain.
- Flank or back pain

7 Toxicity grading

The National Cancer Institute (NCI) common terminology criteria for adverse events (CTCAE) has graded HC from grade 1 to 5 based on level of intervention required (table 2).

Table 2 - NCI CTCAE v 5.0 grading cystitis non-infective

Grade 1	Grade 2	Grade 3	Grade 4
Microscopic haematuria Minimal increase in frequency/urgency Dysuria or nocturia New onset of incontinence	Moderate haematuria Moderate increase in frequency, urgency, dysuria, nocturia, or incontinence Urinary catheter placement or bladder irrigation indicated Limiting instrumental activities of daily living	Gross haematuria Transfusion, intravenous medications, or hospitalization indicated Elective invasive intervention indicated	Life-threatening consequences Urgent invasive intervention indicated

8 Examination / Investigations

- Thorough clinical and medication history – exposure to SACT, pelvic RT, recent intravesical treatment, current immunosuppression status.
- Full blood count (FBC), liver function test (LFTs), urea & electrolytes (U&Es)
- Midstream urinalysis (MSU) - in transplant patients request additional urine sample for BK virus PCR.
- Clinical assessment of bladder symptoms, including:
    - Frequency and amount of urine passed
    - Sense of incomplete voiding
    - Poor urinary stream
    - Intermittent flow
    - Hesitancy
- Physical examination, including palpation of lower abdomen for signs of distended bladder (may consider post-void bladder scan).
- If severe symptoms or uncertain diagnosis > discuss with urology regarding cystoscopy, USS KUB, CT or MRI urogram.

- **Exclude** menstrual period in female patients.
- **Exclude** infection.
- **Exclude** thrombocytopenia or disseminated intravascular coagulation (DIC).
- **Exclude** genitourinary (GU) surgery / interventional radiology (IR) procedure and complication.
- **Consider possibility of malignancy -** Cystoscopy and/or urine cytology may be helpful.

9 Treatment

There is no consensus on the optimal management of HC. Treatment varies depending on the severity and should be individualised for each patient.

In the presence of thrombocytopenia, maintain platelets >50.

In the case of infection, appropriate antimicrobial or antiviral treatment must be administered in line with Trust antimicrobial guidance, in the absence of guidance microbiology/infectious disease can advise on appropriate agent.

Late-onset viral HC will require treatment of the underlying infection as well as symptom management.

Presence of active infection should normally result in delay of SACT treatment until resolution – discuss with the responsible team and consultant.

9.1 Recommended mesna bolus dose

Mesna 1 gram IV in 250mls of sodium chloride 0.9% over 15 - 30 minutes

Oral mesna is not recommended for management of symptoms.

9.2 Bladder pain and/or spasm

Consider anti-spasmodic therapy: Oxybutynin PO 5mg TDS (reduce to 5mg PO BD in the elderly).

9.3 Actions based on urine dip

See management flowchart above and utilise in conjunction with management guidance below.

Test Result	Action
Trace	No action.
+	Re-test. If positive on more than one consecutive test, consider bolus mesna. Check fluids and any concurrent mesna is running correctly or oral doses have been taken. Encourage fluids.
++ / +++	Administer additional IV mesna bolus dose. Double dose of any concurrently running IV mesna. Ambulatory patients should be considered for admission for IV bolus and/or increased infusional mesna until haematuria resolved. Repeated ++ / +++ result, or evidence of macroscopic haematuria should prompt pause and review of current treatment.

9.4 Management based on symptomology / grading

9.4.1 Managing grade 1 - mild symptoms

Microscopic haematuria and/or minimal increase in upper urinary tract symptoms

Hydration – Advise at least 2 L of fluid a day and to void at first sensation.

Oral fluids should be ingested prior to sleep, and patients should awaken once during the night to empty the bladder. Men should be encouraged to stand to void rather than using a bedside urinal in a recumbent position.

Urine output - Maintain output of 100 mL/hr
Fluid balance - Maintain positive fluid balance of 1 to 2 litres/24hrs.
If there is + (one plus) blood:

- No immediate action. Continue monitoring the patient carefully.
- Continue infusion, ensure any fluids and mesna are running appropriately in accordance with SACT regimen.
- If positive on more than 1 consecutive test consider additional IV/PO mesna bolus.

If there is ++ (two plus) blood:

- Administer bolus mesna. Patients requiring bolus mesna should have their infusional mesna or oral doses doubled for all subsequent SACT treatments.
- Repeated ++ result should prompt pause and review of current treatment.

9.4.2 Managing grade 2 or 3 – moderate to severe symptoms

Moderate or gross haematuria and/or moderate to severe increase in upper urinary tract symptoms

Administer Mesna bolus - Administer IV mesna bolus dose. Patients requiring bolus mesna should have their infusional mesna or oral doses doubled for all subsequent SACT treatments.

If ++ dips persist after mesna or there is +++ blood

- Stop cyclophosphamide/ifosfamide (or other suspected causative agent).
- Assess haemodynamic stability
- Optimise IV hydration (e.g. Normal saline 125 mL/hr)
- Ensure adequate bladder voiding
- Consider transfusion if drop in haemoglobin

Additional actions if patient is passing blood clots in urine:

- Consult urology on-call team
- Initiate continuous bladder irrigation with normal saline.
- Consider cystoscopy exploration under anaesthesia to extract clots and identify or treat bleeding areas of mucosa
- Further intervention: Limited evidence exists for instillation of astringents. Interventions such as iliac artery embolization, temporary or permanent urinary diversion and/or cystectomy should be led by a consultant urologist and MDT following failure of other measures to control bleeding.

9.4.3 Practical advice for doubling mesna infusion doses

To increase infusional mesna from 3000 mg/m^2 to 6000mg/m^2 the additional 3000 mg/m^2 of mesna can be put into a separate 1 Litre bag of 0.9% sodium chloride and run alongside the existing mesna and chemotherapy bag.

Increases can be prescribed and started immediately; however, it is essential to discuss with/inform the treating specialist team (e.g. sarcoma/lymphoma). The registrar on call should be involved in the assessment and prescribing for these patients.

10 Prevention of haemorrhagic cystitis

10.1 Prevention

- Encourage hydration
- Encourage frequent urination
- Avoid alcohol, caffeine, and spicy foods.
- Avoid concurrent administration of other bladder-irritant medication.
- Prescribe prophylactic mesna to patients receiving ifosfamide/cyclophosphamide infusions in line with Section 14. This is usually a part of the Aria prescription.

10.2 Monitoring

- Check and document baseline urine dip prior to treatment
- Check urine by dipstick at every void for haematuria and document on EPR.
- Document accurate fluid intake and output on EPR.
- Oral fluid intake = as per ‘hydration’ section above
- Maintain a urine output of 100 mL/hr
- Maintain positive fluid balance of 1-2 Litres/24hours.

11 Monitoring fluid balance

When fluid balance monitoring is necessary, it should be clearly communicated to the nursing team involved in the care of the patient.

It is essential that the fluid balance chart is used by all caregivers for accuracy.

Instructions for recording fluid input and output on EPR is found on the OUH Intranet under the EPR section and as a video recording.

11.1 When to record fluid balance

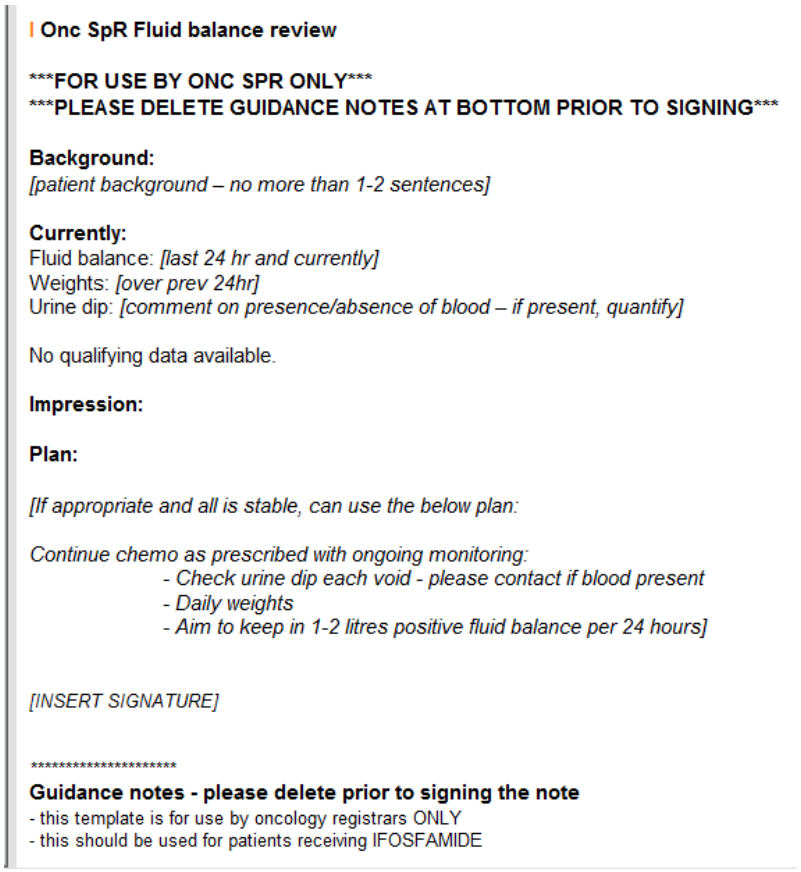
- Patients receiving high-dose methotrexate (> 1g/m2)
- Patients receiving continuous ifosfamide
- Other newer SACT agents if indicated in protocol (e.g. tebentafusp**)**
- When clinically indicated – e.g. fluid restriction, diarrhoea, acute illness

11.2 Medical documentation

There are currently 2 pre-configured powernote templates to assist recording and management of fluid balance on Oncology Ward:

- ‘Onc SpR Fluid Bal r/v – MTX’ – for use with high-dose methotrexate
- ‘Onc SpR Fluid Bal r/v – IFOS’ – for use with ifosfamide

Patients must have their fluid balance reviewed daily. The current fluid balance, weight of patient and urine dip status should be documented.



Onc SpR Fluid balance review

FOR USE BY ONC SPR ONLY
PLEASE DELETE GUIDANCE NOTES AT BOTTOM PRIOR TO SIGNING

Background:
[patient background – no more than 1-2 sentences]

Currently:
Fluid balance: *[last 24 hr and currently]*
Weights: *[over prev 24hr]*
Urine dip: *[comment on presence/absence of blood – if present, quantify]*

No qualifying data available.

Impression:

Plan:

[If appropriate and all is stable, can use the below plan:

Continue chemo as prescribed with ongoing monitoring:
- Check urine dip each void - please contact if blood present
- Daily weights
- Aim to keep in 1-2 litres positive fluid balance per 24 hours]

[INSERT SIGNATURE]

****
Guidance notes - please delete prior to signing the note
- this template is for use by oncology registrars ONLY
- this should be used for patients receiving IFOSFAMIDE

Figure 1 – Example of fluid balance documentation on EPR

12 Interpretation of the urine dip

Within normal working hours inform the relevant specialty team of any positive blood dip, or other significant finding. Ensure the results of the urine dip have been recorded on EPR.

Outside of normal hours, the on-call registrar should be contacted, informed of the result and advised the patient requires a review.

12.1 Methylene blue

Use caution when interpreting urine dips in patients who are receiving treatment with methylene blue.

Methylene blue discolours urine resulting in a blue-green hue, haematuria without clotting can be difficult to discern. It is advised to use a low threshold to treat in presence of symptoms or positive blood on urine dip.

12.1.1 Urine discolouration mimicking appearance of haematuria

Some drugs and foods may discolour the urine and mimic the appearance of haematuria, especially when ingested in large quantities:

- Rifampicin
- Iron supplements
- Nitrofurantoin

- Beetroot
- Blackberries
- Senna
- Metronidazole
- Ketamine
- Chemotherapy drugs (e.g. daunorubicin and doxorubicin).

13 Mesna

Prophylactic mesna doses will usually be pre-built into the Aria prescription.

Mesna interacts with the urotoxic metabolite acrolein to reduce the incidence of cyclophosphamide and ifosfamide-induced haemorrhagic cystitis. Mesna does not reduce the anti-tumour effect of cyclophosphamide or ifosfamide.

Mesna must be present in the bladder at the time of SACT administration to be effective and should continue for the duration of the regimen and up to 12 to 24 hours post-administration. This allows for the concentration of the urotoxic metabolites to fall to non-toxic levels.

Various mesna dosages have been used in practice. Our guidance represents the common institutional standard at Oxford. Please check details of the specific SACT protocol in use at Chemotherapy (SACT) - thamesvalleycanceralliance.nhs.uk or NSSG - Haematology..

13.1 Preventative use with ifosfamide

Short ifosfamide infusion (e.g. 4-hour infusion)

- Administration of oral mesna as an initial dose is not recommended.
- Prior to starting a new ifosfamide infusion, intravenous mesna should be dosed at 20% of the total daily ifosfamide dose and administered as an IV bolus.
- Throughout ifosfamide infusion IV mesna should be concurrently administered in a 1:1 ifosfamide:mesna dose ratio, a small variation in dose is acceptable and common to allow for dose banding and economic use of vials.
- Post-infusion IV mesna can be repeated as 20% of the total daily ifosfamide dose at 4 and 8 hours. If oral mesna is used post-infusion this should be at 40% of the total daily ifosfamide dose at 2 and 6 hours.

Continuous ifosfamide infusion

- Administration of oral mesna as an initial dose is not recommended.
- Prior to starting a new ifosfamide infusion, intravenous mesna should be dosed at 20% of the total daily ifosfamide dose and administered as an IV bolus.
- Throughout ifosfamide infusion IV mesna should be concurrently administered in a 1:1 ifosfamide:mesna dose ratio, a small variation in dose is acceptable and common to allow for dose banding and economic use of vials.
- Post-ifosfamide: Mesna is given as a further 12-hour infusion of 60% of the total daily ifosfamide dose. Total mesna dose = 180% of the ifosfamide dose. Some protocols currently use higher mesna dosing for a longer timeframe.

13.2 Preventative use with cyclophosphamide

Mesna is not routinely given to patients receiving <1 g/m^2 cyclophosphamide, unless there are pre-existing risk factors present to increase risk of bladder irritation.

Standard dose cyclophosphamide

- Prior to starting a new ifosfamide infusion, mesna should be dosed at 20% of the total daily ifosfamide dose. If administered orally, this should be given 2 hours prior to the cyclophosphamide.
- Post-infusion: Oral mesna is dosed at 40% of the cyclophosphamide dose and given 2- and 6-hours following treatment completion. If administered intravenously a 20% dose can be given at 4- and 8-hours post.

High-dose cyclophosphamide (e.g. > 50 mg/kg or >1.5 g/m^2)

- **Bone marrow transplantation:**
  - IV mesna is administered at 40% of the total daily cyclophosphamide dose given four times at three hourly intervals (0, 3, 6 and 9 hours). (Total dose = 160% (w/w) of the oxazaphosphorine dose).
- **Cyclophosphamide priming:**
  - Follows same protocol as standard dose cyclophosphamide, with the exception that mesna must not be omitted from treatment.

13.3 Switching IV to oral mesna post-chemotherapy

When directly switching preparations, the dose of oral mesna should be double that of intravenous mesna unless specified below.

Patients may sometimes be swapped to oral mesna to facilitate early discharge. This switch should be authorised by the treating consultant.

Patient criteria:

- Patient is clinically well, not vomiting and can satisfactorily drink the necessary target fluid volumes
- Patient has adequate urine flow

Fluid calculation:

- It is important for patients to continue hydrating well following discharge. In adult patients, at least 1 litre oral fluid should be consumed following end of chemotherapy infusion.

Oral mesna requirement:

- Infusional mesna may be replaced by oral mesna taken at the point when ifosfamide/mesna or cyclophosphamide infusion completes, then at 2 and 6 hours afterwards.
- All oral mesna doses should be 40% of the total daily ifosfamide or cyclophosphamide dose.

Endorse instructions on Aria and prescribe in full on EPMA TTO for discharge. If outside of normal business hours – contact on-call pharmacist to discuss plan. Refer pharmacy to this document (via intranet) for advice.

Monitoring

- There is no requirement for the patient to be sent home with urine dipsticks for haematuria monitoring. If this is considered a risk, do not discharge the patient home.

13.4 Vomiting within 2 hours of oral mesna

If patients vomit within two hours of taking a dose of oral mesna, they should repeat the dose or receive an intravenous dose of mesna.

13.5 Oral use of mesna ampoules

Mesna ampoules have been shown to be effective when taken orally. Compared with intravenous administration, overall availability of mesna in urine after oral administration is approximately 50%; the onset of urinary excretion is delayed by up to 2 hours and is more prolonged than following intravenous dosing.

The ampoules can be diluted in a flavoured drink such as orange juice or cola. This mixture is stable when refrigerated in a sealed container for 24 hours.

13.6 Possible side-effects

Mesna in doses of up to 70 – 100 mg/kg IV were shown to produce no toxic effect on bone marrow, hepatic, renal or CNS functions.

Vomiting and diarrhoea only occurred after doses greater than 80 mg/kg.

Very common adverse reactions (> 10%):

- Headache
- Infusion site reactions
- Abdominal pain/colic
- Light-headedness
- Lethargy/drowsiness
- Rash
- Diarrhoea
- Nausea
- Flushing
- Influenza-like illness.

Anaphylaxis, bullous skin reactions, and drug rash with eosinophilia and systemic symptoms (DRESS) have been reported rarely. Consult the product SPC or online BNF for a full list of adverse effects.

13.7 Treatment interruptions

Where SACT administration has been temporarily/unintentionally interrupted (e.g. a gap in administration of continuous ifosfamide), mesna infusion must continue so that bladder protection is maintained.

A temporary prescription for IV mesna may be required on the inpatient chart until the aria prescription is resumed.

It is **not necessary** to maintain the 1:1 ratio SACT-mesna dosing when SACT is not being infused.

For most patients on infusional ifosfamide (3 g/m^2/day), mesna can be prescribed temporarily as **1 g/m^2 IV over 6 hours** or **2 g/m^2 IV over 12 hours** until resumption of therapy.

14 Review

This guideline will be reviewed at least every 3 years.

15 References

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