

Guidelines for the administration of Mesna with Ifosfamide and Cyclophosphamide

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1.0 Introduction

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The alkylating agents ifosfamide and cyclophosphamide are oxazaphosphorine agents that have important roles in the treatment of several types of cancer. Ifosfamide and high-dose cyclophosphamide may produce haemorrhagic cystitis as a dose limiting toxicity. Both cyclophosphamide and ifosfamide are pro-drugs that undergo metabolic activation via liver P-450 microsomes to both active and inactive metabolites. The metabolites acrolein and 4-hydroxyifosfamide have been implicated as the major causative agent in oxazaphosphorine induced urothelial toxicity.

Mesna (sodium-2-mercaptoethane sulphonate) is used clinically to prevent the urinary tract toxicity caused by the active metabolites.

2.0 Objectives

The objectives of these guidelines are to promote consistent clinical practice in relation to the use of mesna in the prevention and treatment of ifosfamide and cyclophosphamide-induced urinary tract toxicity.

3.0 Scope

This guideline is relevant to:

- Oncology and haematology doctors
- Oncology and haematology nurses
- Pharmacists
- Other staff involved in the administration of ifosfamide or cyclophosphamide

4.0 Duties

All medical and support staff responsible for the care of patients undergoing treatment with ifosfamide or cyclophosphamide are required to familiarise themselves with this policy to ensure seamless care in the event of such urinary tract toxicity occurring.

5.0 Guidance

5.1 Background

The overall reported incidence of oxazaphosphorine-induced haemorrhagic cystitis varies considerably due to a lack of agreement for diagnostic criteria, variability in definition of the relevant time frame, and uncertainty regarding the relative contributing factors such as thrombocytopenia, concurrent or previous chemotherapy or radiotherapy, and viral infections. It is suggested that in patients treated with ifosfamide without urothelial protection the overall incidence of haemorrhagic cystitis ranges from 18% to 40% and is considered dose-limiting. Among patients treated with high-dose cyclophosphamide with aggressive hydration in the bone marrow transplantation setting, the reported incidence of severe haemorrhagic cystitis ranges from 0.5% to 40%. The incidence of haemorrhagic cystitis is considerably lower with cyclophosphamide as compared with ifosfamide and so mesna use is unnecessary with standard doses of cyclophosphamide i.e. $1\text{g}/\text{m}^2$.

5.2 Rationale for the use of mesna

Mesna is a thiol compound, which functions as a regional detoxicant of the oxazaphosphorine metabolites. After oral or intravenous administration, mesna undergoes rapid oxidation in the plasma to dimesna. Only a small portion of the dose remains in the circulation as the physiologically active compound. Both mesna and dimesna are very hydrophilic and therefore remain in the intravascular compartment, where they are rapidly cleared by the kidneys. The free sulfhydryl (thiol) groups of mesna combine directly with a double bond of acrolein and with other urotoxic 4-hydroxy-oxazaphosphorine metabolites to form stable nontoxic compounds. Because urinary mesna concentration greatly exceeds plasma mesna concentrations regional detoxification of urotoxic oxazaphosphorine metabolites occurs in the urinary system. This restriction of mesna to the urinary system implies that mesna neither protects against non-urologic toxicities of oxazaphosphorines nor interferes with their cytotoxic activity. Mesna in doses of up to 70-100mg/kg IV was shown to produce no toxic effect on bone marrow, hepatic, renal or CNS functions. Vomiting and diarrhoea only occurred after doses greater than 80mg/kg.

5.3 Patient eligibility

Mesna should be used for all patients receiving ifosfamide and high dose cyclophosphamide (>1g/m²).

5.4 Prescribing information for mesna

These are general principles followed for the majority of regimens used at UCLH but they may not represent all regimens currently in use.

5.4.1 Mesna dosing with ifosfamide

Day 1

Mesna equivalent of 20% total daily ifosfamide dose given as IV bolus pre-ifosfamide

Mesna equivalent of 100-120% total daily ifosfamide dose given as IV infusion over 24 hours

Day 2+

Mesna equivalent of 100-120% total daily ifosfamide dose given as IV infusion over 24 hours

Final day

Pre ifosfamide

Mesna equivalent of 40% total daily ifosfamide dose given as IV bolus pre-ifosfamide

Post ifosfamide

Mesna equivalent of 40% total daily ifosfamide dose given as IV bolus post-ifosfamide

Mesna equivalent of 40% total daily ifosfamide dose given **orally** 2 and 6 hours after the end of the ifosfamide infusion. (3 doses are supplied in case of vomiting)

Time from end of ifosfamide infusion	Route	Dose of Mesna	Example
T ₀	iv bolus	40% daily ifosfamide dose	3g/m ² ifosfamide =1200 mg/m ² mesna.
T _{2hr}	po	40%	3g/m ² =1200mg/m ² oral mesna
T _{6hr}	po	40%	3g/m ² =1200mg/m ² oral mesna

N.B. Mesna tablet strengths: 400 mg or 600mg. Round up dose if necessary

Or if unsuitable for oral mesna equivalent of 100-120% total daily ifosfamide dose given as IV infusion to run for at least 12 hours post end of ifosfamide infusion.

NB Advise patient to drink at least 2 litres of fluid on the final day.

5.4.2 Mesna dosing with high dose cyclophosphamide (>1g/m²)

Conditioning regimens prior to HSCT (cyclophosphamide 60mg/kg)

Mesna equivalent of 50% total dose cyclophosphamide given as IV bolus pre cyclophosphamide and at 3, 6 and 9 hours after the start of the cyclophosphamide infusion.

HSCT mobilisation (cyclophosphamide 1.5g/m²)

Mesna equivalent of 20% total daily cyclophosphamide dose given as IV bolus pre-cyclophosphamide

Mesna equivalent of 40% total daily cyclophosphamide dose given orally 2 and 6 hours after then start of the cyclophosphamide infusion. (3 doses are supplied in case of vomiting)

5.4.3 Administration by continuous infusion

Mesna is added to either:

3 litre bags of glucose 2.5%, sodium chloride 0.45% + potassium chloride 80mmol to run over 24 hours (via CADD prizm pump in backpack) or

4 x 1 litre bags of glucose 2.5%, sodium chloride 0.45% + potassium chloride 20mmol/L to run over 6 hours each. (Total daily dose to be divided into the 4 bags).

5.4.4 Bioavailability

After oral administration mesna has a bioavailability of 50-75% and the urinary mesna concentrations are approximately one half of those observed after IV infusion.

6.0 Haematuria

Haemorrhagic cystitis is generally graded as mild, moderate or severe according to the degree of pain and haematuria. Severe haemorrhagic cystitis typically includes the presence of gross haematuria with clots and occurrence of clinical complications; it can be extremely painful and debilitating, requiring prolonged and expensive hospitalisation.

6.1 Monitoring for haematuria

Patients should always have their urine tested by dipstick for blood prior to starting ifosfamide or cyclophosphamide. This will provide a baseline level from which to assess any haematuria that may occur. Thereafter urine should be tested with each sample.

6.2 Presentation of haematuria

6.2.1 Prior to the start of the ifosfamide or cyclophosphamide infusion

An unexplained positive test for blood prior to treatment should be investigated. Once other causes of haematuria have been excluded, for example urinary tract infection or menstruation, take a spot urine sample for microscopy for red cells in order to exclude false positive results. Results should be awaited before commencing ifosfamide or cyclophosphamide.

If cause identified further testing of urine may be unnecessary due to false positive results.

6.2.2 Whilst receiving intravenous mesna hydration.

Exclude other causes of haematuria, for example urinary tract infection or menstruation. Take a spot urine sample for microscopy for red cells in order to exclude false positive results and follow the guidelines below

Test result	Action
Trace	Re-test
+	Re-test If '+' on more than one consecutive test give additional bolus mesna
++	Double intravenous mesna
+++	Double intravenous mesna

These test results are all as 'above baseline' results.

Once a decision has been made to give additional intravenous mesna

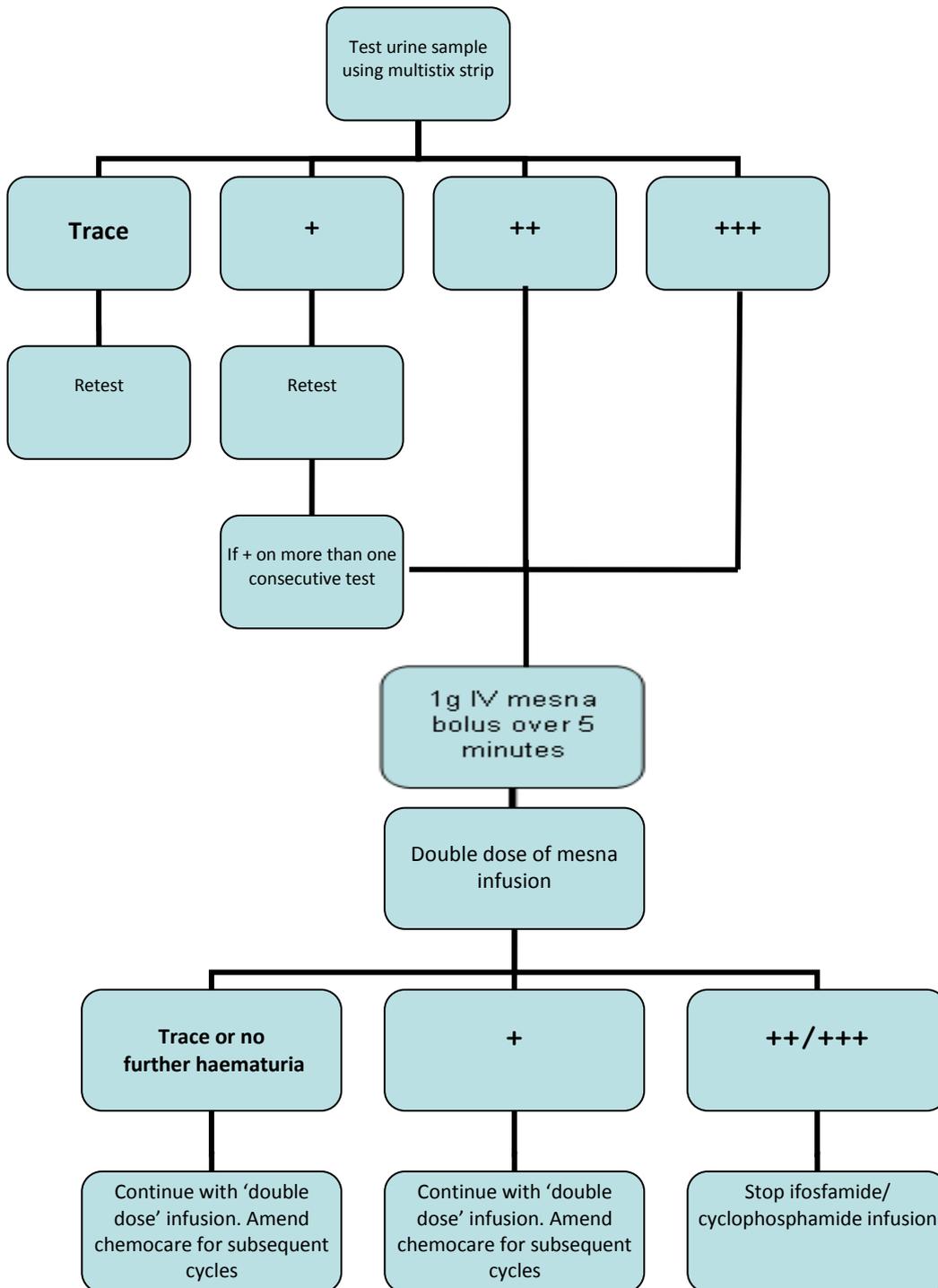
1. Disconnect fluids.
2. Give an additional dose of 1g mesna bolus IV over 5 minutes.
3. Prescribe double the original dose of infusional mesna and continue infusion

6.2.3 Doubling mesna doses

The mesna hydration bag currently running should be stopped and replaced with a new bag containing double the amount of mesna and run for the time remaining i.e. until next ifosfamide due or providing there is no sign of haematuria until a minimum of 12 hours after final ifosfamide infusion.

NB ensure that future bags/ backpacks are prescribed with the increased dose

Algorithm for haematuria whilst receiving intravenous mesna hydration



6.2.4 Whilst receiving oral mesna

Patients who are switched to oral mesna for discharge should be educated to test their urine for up to 12 hours after the end of the ifosfamide/cyclophosphamide infusion.

For patients experiencing haematuria after discharge on oral mesna the following guide should be followed:

Test result	Action
Trace	Re-test
+	Re-test If '+' on more than one consecutive test give intravenous mesna
++	Admit for intravenous mesna
+++	Admit for intravenous mesna

These test results are all as 'above baseline' results.

An extra dose of oral mesna will be supplied to patients to be taken if an episode of vomiting is experienced while taking their regular oral mesna dose. Consider advising taking this dose (if not already taken) in addition to being admitted to hospital.

An intravenous mesna bolus followed by a continuous infusion as per previous days should be given and continued until haematuria resolved.

Consideration should also be given to the suitability of the patient for oral mesna with further cycles of ifosfamide.

7.3 Subsequent courses

If higher doses of IV mesna or a switch from oral to IV mesna were required during a treatment cycle and were effective at preventing further haematuria ensure future prescriptions on Chemocare® are amended as appropriate and document on treatment notes.

8.0 References

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