

## **GUIDELINES FOR THE PREVENTION AND TREATMENT OF CHEMOTHERAPY REGIMEN SPECIFIC COMPLICATIONS – INTRAVENOUS HYDRATION FLUIDS**

### **INTRODUCTION**

Chemotherapy that has renal or uroepithelial toxicity requires accompanying intravenous hyper-hydration. The following drugs must be given with intravenous hyper-hydration:

- Cisplatin
- Ifosfamide
- Cyclophosphamide at daily doses > 1g/m<sup>2</sup>
- Methotrexate at doses > 1g/m<sup>2</sup>
- Melphalan

**\*\*PLEASE REFER TO PATIENT'S INDIVIDUAL CHEMOTHERAPY PROTOCOL FOR FULL DETAILS OF INTRAVENOUS HYDRATION FLUID REQUIREMENTS\*\***

These guidelines cover:

- Pre and post hydration requirements
- Specific supportive care for cisplatin, ifosfamide/cyclophosphamide, melphalan and high dose methotrexate.

Hydration may also be required:

- To treat or prevent acute tumour lysis syndrome (see Acute Tumour Lysis Syndrome (TLS) Guidelines for the Prevention and Management)
  - Note: patients may be at risk of tumour lysis syndrome prior to confirmation of diagnosis. Potassium containing fluids should therefore be avoided until the risk of tumour lysis is known.
- In patients who have inadequate oral intake during any chemotherapy administration (in addition to the drugs listed above). Refer to Clinical Guideline on the Administration of Intravenous Fluids.

### **RECOMMENDED FLUIDS**

Fluids used alongside chemotherapy include:

- 5% glucose and 0.45% sodium chloride (available as 500ml bags)
- 2.5% glucose, 0.45% sodium chloride and potassium chloride 20mmol/L (available as 1L, 2L and 3L bags)
- 5% glucose, sodium chloride 0.45% and potassium chloride 20mmol/L (available as 500ml bags)
- 2.5% glucose, 0.45% sodium chloride, potassium chloride 20mmol/L, magnesium sulfate 10mmol/L and calcium chloride 0.6mmol/L (available as 1L bags). In the event of a disruption in supply of these bags, magnesium may be added to 2.5% glucose, 0.45% sodium chloride and potassium chloride 20mmol/L (calcium may be omitted).

The choice of fluid depends on:

- Compatibility with the rest of the chemotherapy cycle
- Risk of hyponatraemia, hypokalaemia or hypomagnesaemia associated with the chemotherapy drug(s).

## **HYPER-HYDRATION RATES**

Hyper-hydration is usually given at 2000-3000ml/m<sup>2</sup>/day (84-125ml/m<sup>2</sup>/hour), taking into account the fluid volumes of the chemotherapy. Higher rates e.g. 200ml/m<sup>2</sup>/hour for 3-4 hours may be required to pre-hydrate patients having cisplatin or melphalan.

The volume of fluid should be capped at 4500ml per day (188ml/hour) unless otherwise stated in the protocol or as clinically indicated.

Note hydration above maintenance requirements can lead to fluid overload. Monitor strict fluid balance. If there is concern about a high positive fluid balance assess for clinical features of fluid overload and treat accordingly.

Renal function should be monitored throughout chemotherapy with hydration. A daily Oncology Profile should be sufficient in most cases.

## **CISPLATIN**

Cisplatin is usually given by intravenous infusion over six to twenty-four hours. Hyper-hydration is required from three hours before until twenty-four hours after completion of infusion. Hydration fluids should contain potassium and magnesium to prevent hypokalaemia and hypomagnesaemia.

Mannitol should be used to force diuresis:

Mannitol 10% is given at a rate of 15ml/m<sup>2</sup>/hour during and for six hours after the end of the cisplatin infusion.

Strict fluid balance is necessary. If urine output falls below 3ml/kg/hour for two hours a short infusion of mannitol 10% 5ml/kg should be given over 15-30 minutes.

Furosemide should be avoided due to additive oto- and nephrotoxicity.

## **CYCLOPHOSPHAMIDE AND IFOSFAMIDE**

Cyclophosphamide and ifosfamide are both prodrugs that are metabolised in the liver to produce the active cytotoxic compound. This metabolism also produces acrolein that is thought to be responsible for haemorrhagic cystitis: mesna protects against this complication by binding to acrolein.

It is essential that children receiving ifosfamide or higher dose cyclophosphamide pass urine at least every 4 hours, as this minimises bladder toxicity. They should be encouraged to pass urine, and if indicated IV furosemide should be given.

Strict fluid balance is required. Urinalysis should be done on every urine to check for blood. It should be noted that mesna can cause false positive results for ketone bodies in dipstick tests.

### **Cyclophosphamide doses > 1g/m<sup>2</sup> and all ifosfamide doses:**

Mesna is given alongside hyper-hydration for cyclophosphamide doses above 1g/m<sup>2</sup> and for all ifosfamide doses. Where there are compatibility issues it may be necessary to interrupt the mesna infusion and give boluses of mesna. Contact the oncology/haematology pharmacist for advice.

Mesna can be given orally at consultant discretion. The bioavailability of oral mesna is 50%.

When prescribing mesna and hydration always refer to the chemotherapy protocol. If this differs from the guidance below, discuss with the oncology/haematology pharmacist or consultant before prescribing.

- Intravenous hydration with 2.5% glucose, 0.45% sodium chloride and potassium chloride 20mmol/L at a rate of 125ml/m<sup>2</sup>/hour (max 188ml/hour) starting 3 hours before cyclophosphamide or ifosfamide and continuing for a minimum of 12 hours after completion of the last dose of cyclophosphamide or ifosfamide.
- Mesna is given alongside intravenous hydration at 120% (mg/mg) of the total daily cyclophosphamide or ifosfamide dose. Mesna syringes are prepared by nursing staff on the ward as follows.
  - Mesna to run alongside pre-hydration will be prepared in 50ml sodium chloride 0.9% for patients >10kg and 24ml for patients < 10kg.
  - Mesna to run alongside post hydration will be prepared in multiples of 48ml:
    - <4800mg will be in one syringe of 48ml over 24 hours at 2ml/hour
    - >4800mg will be evenly split into 2 x 48ml syringes, each to run over 12 hours at 4ml/hour

#### **Cyclophosphamide 300mg/m<sup>2</sup> – 1g/m<sup>2</sup>**

- Mesna is not required
- Intravenous hydration at 125ml/m<sup>2</sup>/hour starting with or before the first cyclophosphamide dose and continuing for at least six hours after the last dose.

#### **Cyclophosphamide < 300mg/m<sup>2</sup>**

- Mesna and intravenous hydration not required, providing there is adequate oral fluid input and micturition is encouraged.

#### **If a patient develops haematuria (2+ or greater on dipstick) whilst receiving cyclophosphamide or ifosfamide**

- Check the fluid regimen to ensure that they are receiving intravenous hydration at rate of 3000ml/m<sup>2</sup>/day (125ml/m<sup>2</sup>/hour). Check with consultant before increasing fluid to more than 4500ml per 24 hours.
- Ensure that they have received mesna as per the guidelines outlined in their specific protocol.
- If a patient is not already receiving mesna, start mesna at 120% of the cyclophosphamide or ifosfamide dose.
- If a child develops haematuria and is already receiving mesna at the appropriate dose, then increase the total daily dose to 160% of the cyclophosphamide or ifosfamide dose.

#### **HIGH DOSE METHOTREXATE**

High dose methotrexate refers to all doses  $\geq 1\text{g/m}^2$ .

Hyper-hydration, sodium bicarbonate and calcium folinate rescue are required alongside high dose methotrexate.

Creatinine & urea must be measured at least daily from admission until calcium folinate rescue is complete (see below). Methotrexate levels are checked after the completion of the methotrexate infusion, the timings of which are dictated by individual protocols.

In the event of renal failure or severely delayed methotrexate clearance, the enzyme glucarpidase is given which inactivates methotrexate. Refer to Guideline for the Use of Glucarpidase (Carboxypeptidase) in Methotrexate Induced Renal Failure.

### **Calcium Folate Rescue**

Calcium folinate rescues normal tissue from methotrexate toxicity. Scheduling of calcium folinate depends on the duration of methotrexate infusion and is dictated by individual protocols. High methotrexate levels require increased doses of calcium folinate.

Sodium levofolinate is available in the event of hypercalcemia. To be commenced on discussion with haematology/oncology consultant only.

### **Hyper-hydration and Sodium Bicarbonate**

Hyper-hydration is required for at least four hours prior to the start of the methotrexate infusion and must continue until calcium folinate rescue is complete.

Sodium bicarbonate is necessary to alkalinise urine and promote excretion of methotrexate. Sodium bicarbonate 8.4% (1mmol/ml) is given alongside hyper-hydration at an initial rate of 6.25mmol/m<sup>2</sup>/hour (some protocols require a rate of 10 mmol/m<sup>2</sup>/hour during pre-hydration). Urine pH should be above 7 prior to commencing methotrexate infusion. If urine pH falls below 7 on two consecutive urine samples, the rate of the sodium bicarbonate infusion should be increased by 20%. If urine pH goes above 8 the rate should be reduced back to the initial rate. Sodium bicarbonate and hyper-hydration should continue until calcium folinate rescue is complete.

### **MELPHALAN**

Hyper-hydration is required alongside melphalan. Urine output of 4ml/kg/hour must be established prior to melphalan administration and maintained for at least 2 hours post dose. The following schedule is recommended:

- T=0 Commence pre-hydration (sodium chloride 0.9%) at 125ml/m<sup>2</sup>/hour (max 188ml/hour) for 3.5 hours
- T=2 Furosemide 0.5mg/kg (max 40mg)
- T=2.5 Furosemide 0.5mg/kg (max 40mg) (if required)
- T=3 Melphalan over 15 mins
- T=3.5 Post hydration at 125ml/m<sup>2</sup>/hour (max 188ml/hour) for 24 hours

Note: Melphalan is not compatible with glucose containing solutions.

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Recommended fluids	1	Preparation of electrolyte hydration	Contingency for disruption to supply
Calcium Folate Rescue	5	Sodium levofolinate added	For patients with hypercalcaemia
Hyperhydration and sodium bicarbonate	5	Increased rate of sodium bicarbonate during prehydration	New protocols
Melphalan	5	Prehydration duration added	For clarity