**Systemic Anti Cancer Treatment Protocol**

# IFOSFAMIDE
## Sarcoma

**PROTOCOL REF: MPHAIFOSF**
**(Version No: 1.0)**

## Approved for use in:

Soft tissue sarcoma
Advanced or metastatic disease

## Dosage:

| Drug | Dosage | Route | Frequency |
|---|---|---|---|
| Mesna | 3g/m$^2$ days on 1, 2 and 3 | IV | Every 21 days |
| Ifosfamide + Mesna | 3g/m$^2$ + 3g/m$^2$ on days 1, 2 and 3 | IV | Every 21 days |
| Mesna | See administration | | Every 21 days |

**Supportive treatments:**

**Anti emetic risk -** Moderate
Dexamethasone tablets, 4mg twice daily for 3 days
Domperidone 10mg oral tablets, up to 3 times a day or as required

## Extravasation risk:

Irritant

## Administration notes:

**Chemotherapy on day 2 to commence 24 hours after day 1 treatment started.**
**And on day 3 to commence 24 hours after day 2 treatment started.**

**Give for up to 6 cycles**

**Consider adding aprepitant if previous problems with nausea/vomiting**

## Administration:

| Day | Drug | Dosage | Route | Diluent and Rate |
|---|---|---|---|---|
| 1 | Ondansetron<br>Immediately prior to mesna infusion | 16mg | PO | |
| 1 | Dexamethasone<br>Immediately prior to mesna infusion | 8mg | PO | |
| 1 | **Mesna** | 3000mg/m$^2$ | IV | In 500mL sodium chloride 0.9% over 1 hour |
| 1 | **Ifosfamide + Mesna** | 3000mg/m$^2$ + 3000mg/m$^2$ | IV | 1000mL sodium chloride 0.9% over 4 hours |
| 1 | **Mesna** | 3000mg/m$^2$ | IV | 1000mL sodium chloride 0.9% over 8 hours |
| 2 | Ondansetron | 16mg | PO | 24 hours after day 1 dose |
| 2 | Dexamethasone | 8mg | PO | 24 hours after day 1 dose |
| 2 | **Mesna** | 3000mg/m$^2$ | IV | In 500mL sodium chloride 0.9% over 1 hour |
| 2 | **Ifosfamide + Mesna** | 3000mg/m$^2$ + 3000mg/m$^2$ | IV | 1000mL sodium chloride 0.9% over 4 hours |
| 2 | **Mesna** | 3000mg/m$^2$ | IV | 1000mL sodium chloride 0.9% over 8 hours |
| 3 | Ondansetron | 16mg | PO | 24 hours after day 2 dose |
| 3 | Dexamethasone | 8mg | PO | 24 hours after day 2 dose |
| 3 | **Mesna** | 3000mg/m$^2$ | IV | In 500mL sodium chloride 0.9% over 1 hour |
| 3 | **Ifosfamide + Mesna** | 3000mg/m$^2$ + 3000mg/m$^2$ | IV | 1000mL sodium chloride 0.9% over 4 hours |
| 3 | **Mesna** | 3000mg/m$^2$ | IV | 1000mL sodium chloride 0.9% over 8 hours |

### Ifosfamide

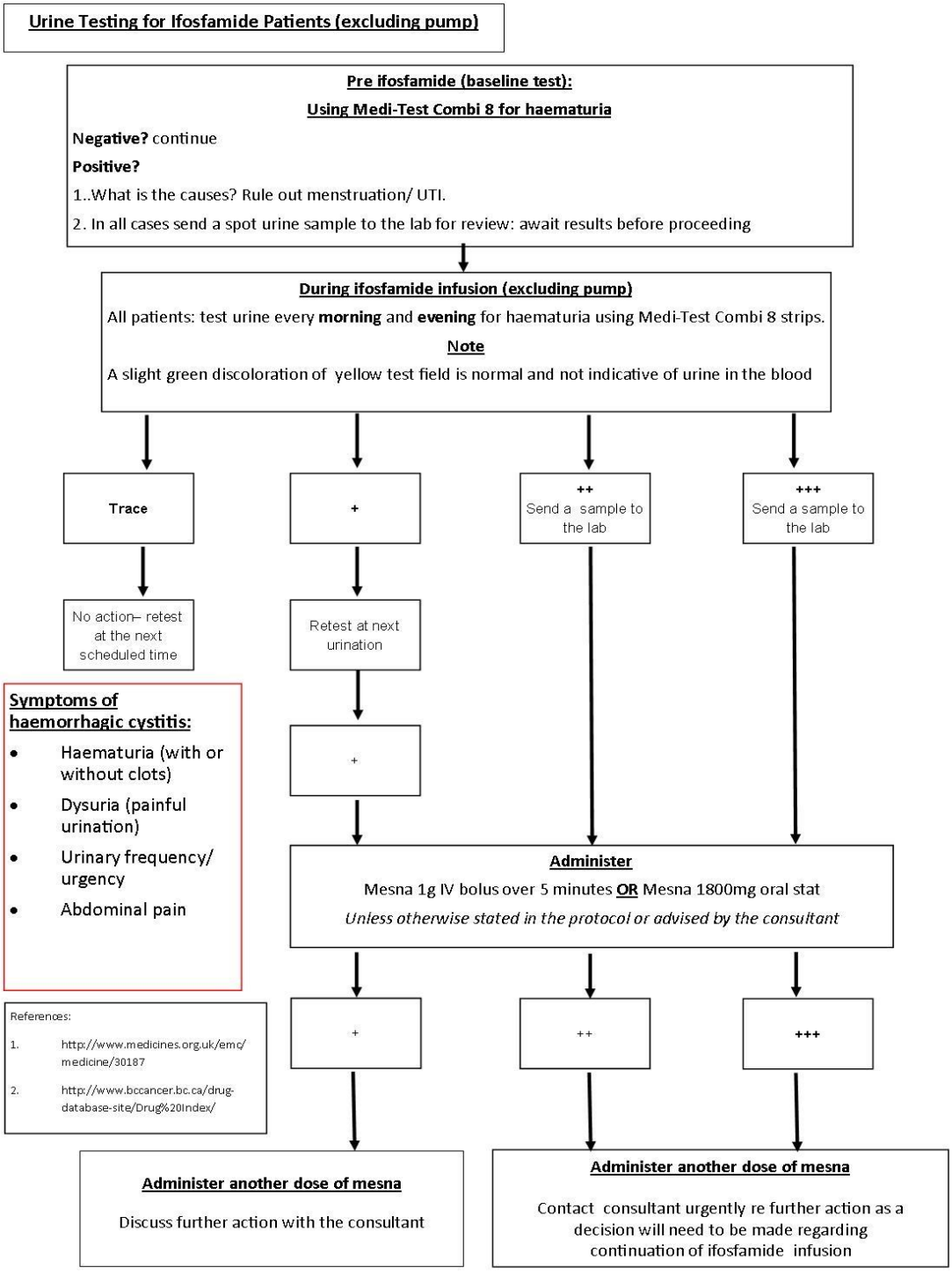
Ensure adequate hydration and that fluids with Mesna are prescribed and administered.
Record patients weight at the same time each day as well as a strict fluid balance chart. If there is a postitive fluid balance of 2 litres or more, weight gain of > 2kg or symptoms of fluid overload give furosemide 20mg orally.
Test urine for microscopic haematuria each cycle (see algorithm)
Observe for insidious signs of encephalopathy, initially somnolence and confusion (see toxicity management)

## Main Toxicities:

Myelosuppression, alopecia, mucositis, nephrotoxicity, central neurotoxicity, haemorrhagic cystitis leading to bladder fibrosis, ovarian failure

## Investigations and treatment plan

| | Pre | Cycle 1 | Cycle 2 | Cycle 3 | Cycle 4 | Cycle 5 | Cycle 6 | Comments |
|---|---|---|---|---|---|---|---|---|
| Medical Assessment | X | | X | X | X | X | X | Every cycle |
| Nursing Assessment | X | X | X | X | X | X | X | Every cycle |
| FBC | X | X | X | X | X | X | X | Every cycle |
| U&E & LFT | X | X | X | X | X | X | X | Every cycle |
| CrCl (Cockroft and Gault) | X | X | X | X | X | X | X | |
| $Ca^{2+}$, $Mg^{2+}$, $Cl^{-}$, $HCO_3$ | X | X | X | X | X | X | X | Every cycle |
| Urine $PO_4$ , creatinine, osmolarity (early morning) | X | | X | | X | | X | Alternate cycles |
| CT scan | X | | | X | | | | As clinically indicated |
| Informed Consent | X | | | | | | | |
| Blood pressure measurement | X | X | X | X | X | X | X | As clinically indicated |
| PS recorded | X | X | X | X | X | X | X | Every cycle |
| Toxicities documented | X | X | X | X | X | X | X | Every cycle |
| Weight recorded | X | X | X | X | X | X | X | Every cycle |
| Urine dipstick (for protein / blood | X | X | X | X | X | X | X | Every cycle (see algorithm) |


Urine Testing for Ifosfamide Patients (excluding pump)
Pre ifosfamide (baseline test):
Using Medi-Test Combi 8 for haematuria
Negative? continue
Positive?
1..What is the causes? Rule out menstruation/ UTI.
2. In all cases send a spot urine sample to the lab for review: await results before proceeding
During ifosfamide infusion (excluding pump)
All patients: test urine every morning and evening for haematuria using Medi-Test Combi 8 strips.
Note
A slight green discoloration of yellow test field is normal and not indicative of urine in the blood
Trace
+
++
Send a sample to the lab
+++
Send a sample to the lab
No action– retest at the next scheduled time
Retest at next urination
+
Symptoms of haemorrhagic cystitis:
Haematuria (with or without clots)
Dysuria (painful urination)
Urinary frequency/ urgency
Abdominal pain
Administer
Mesna 1g IV bolus over 5 minutes OR Mesna 1800mg oral stat
Unless otherwise stated in the protocol or advised by the consultant
References:
1. http://www.medicines.org.uk/emc/medicine/30187
2. http://www.bccancer.bc.ca/drug-database-site/Drug%20Index/
+
++
+++
Administer another dose of mesna
Discuss further action with the consultant
Administer another dose of mesna
Contact consultant urgently re further action as a decision will need to be made regarding continuation of ifosfamide infusion

## Dose Modifications and Toxicity Management:

### Haematological toxicity

Proceed on day 1 if all apply:-

| | |
|---|---|
| ANC ≥ 1.0 x $10^9$/L | Platelets ≥ 100 x $10^9$/L |

Delay 1 week on day 1 if any apply:-

| | |
|---|---|
| ANC ≤ 0.9 x $10^9$/L | Platelets ≤ 99 x $10^9$/L |

Dose at week 2 will depend on the lowest blood count the previous week

| Parameter | Action |
|---|---|
| Neutrophils 0.5 – 1.0 x $10^9$/L **Or** platelets 25 – 99 x $10^9$/L | Delay treatment for one week, if FBC on week two within normal parameters: continue with full dose treatment |
| Neutrophils < 0.5 x $10^9$/L **Or p**latelets < 25 x $10^9$/L | Delay treatment for one week, if FBC on week two within normal parameters: continue with 75% dose of ifosfamide |
| Any neutropenic sepsis | Delay until full recovery<br>Continue with a 75% dose of ifosfamide if appropriate |

### Non-haematological toxicity

**Renal**

Measure serum creatinine each cycle and calculate CrCl using Cockroft and Gault

| GFR (mL/min) | Ifosfamide dose |
|---|---|
| Above 60 | 100% |
| 40 to 59 | 70% |
| Below 40 | Clinical decision |

Measure serum electrolytes and bicarbonate levels and calculate tubular function (Tp/Ccrea) before each cycle of ifosfamide

$$Tp/C_{creat} = \frac{PO_{4serum} - PO_{4urine} \times SrCr_{\mu mol/l}}{Creatinine_{Urine}}$$

| Toxicity Grade* | GFR (ml/min/1.73m2) | TpCreat (mmol/L) | $HCO_3$* (mmol/L) | Action (apply worst grade) |
|---|---|---|---|---|
| Grade 0/1 | ≥60 | ≥1.00 | ≥17.0 | Continue Ifosfamide at 100% dose |
| Grade 2 | 40 - 59 | 0.80 – 0.99 | 14.0 – 16.9 | Ifosfamide 70% dose |
| Grade 3 | ≤40 | ≤0.80 | ≤14.0 | Use cyclophosphamide** instead dose 1500mg/$m^2$/d, day 1 only |

| | |
|---|---|
| *Check low values of $HCO_3$ when patient is clinically stable to exclude e.g. infection as a cause before modifying ifosfamide dose / treatment<br>****Always discuss / check with consultant to confirm before substituting cyclophosphamide 1500mg/m$^2$ d1 for ifosfamide.** | |
| **Hepatic** | **Ifosfamide** – note that ifosfamide is generally not recommended if bilirubin > ULN or ALP > 2.5 ULN – discuss with consultant if this is the case. Note that in the reference trial patients were eligible for full dose treatment if bilirubin < 30micromol/L.[1] |
| **Neurotoxicity** | **Central**<br>Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass.<br><br>Note that most mild cases of encephalopathy will resolve spontaneously in 24 to 72 hours.<br><br>If CTC grade 3 or 4 central neurotoxicity occurs (somnolence 30% of the time, disorientation / hallucination / coma or seizures on which consciousness is altered etc)<br>**Stop Ifosfamide infusion**<br>consider the use of methylene blue (methylonium) 50mg IV infusion as follows:<br><br>50mg (5ml ampoule of 1% solution) every 4 hours, by IV slow bolus<br><br>Patients who have had an episode of ifosfamide enduced encephalopathy in a previous cycle should be treated as follows:<br><br>Give one dose of 50mg (5ml ampoule of 1% solution) IV slow bolus 24 hours prior to ifosfamide. During ifosfamide infusion give 50mg (5ml ampoule of 1% solution) IV slow bolus every 6 hours during the infusion.<br><br>If repeated grade 3 or 4 central neurotoxicity occurs consider withholding ifosfamide and substitute cyclophosphamide 1500mg/m$^2$ on d1 only |
| **Mucositis** | Grade 3 or 4 – defer treatment until recovery, reduce subsequent doses by 20% |

### Cockroft and Gault formula

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

## References:

Judson et al, Doxorubicin alone vs intensified doxorubicin plus ifosfamide for 1st line treatment of advanced or metastatic soft – tissue sarcoma: a randomised phase 3 trial, Lancet Oncology, volume 15, No4, p415-423, April 2014
Summerhayes and Daniels, Practical Chemotherapy, 2003
[1]Lorigan, P et al; JCO 2007; 25 (21): 3144-31