SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Ifosfamide + Mesna PUMP Sarcoma

PROTOCOL REF:
(Version No. MPHAIMPS

Approved for use in:

Soft tissue sarcoma

Advanced or metastatic disease

Allows avoidance of inpatient chemo admissions

Dosage:

Drug	Dose	Route	Frequency
Ifosfamide + Mesna **PUMP**	over 7 days via LV1.5 BSA 1.40m^2 to 1.60m^2 Ifosfamide 10,560mg + Mesna 10,600mg BSA 1.61m^2 to 1.80m^2 Ifosfamide 12,000mg + Mesna 10,000mg BSA 1.81m^2 to 2.00m^2 Ifosfamide 13,040mg + Mesna 9,000mg	IV	D1 + D8
Mesna ORAL	1000mg/m^2 ONCE a day for 14 days	PO	D1 to D14
Mesna ORAL	1600mg to be taken as directed when blood present in urine	PO	D1 to D14

28 day cycle for a maximum of 6 cycles.

Provides 14 days of continuous treatment.

Mesna PO dose banded to nearest 200mg (available as 400mg or 600mg tablets).

Counselling Points:

Encephalopathy

Encephalopathy is a rare but serious complication of ifosfamide treatment. Patients and carers should be counselled to recognise the early signs. These include

- Drowsiness
- Altered mental state; include confusion, an inability to concentrate, impaired memory

Progressive loss of consciousness

Urine Dipstick Testing

Testing for blood should take place TWICE daily for 14 days. Positive results should be managed according to the flow diagram.

Pregnancy

Ifosfamide has been show to damage foetal development in animal models.

Ifosfamide can also affect the fertility of men and women and has the potential to lead to sterility. Sperm or egg banking may be explored prior to treatment for those wishing to have children

Effective contraception should be used during ifosfamide treatment and continued following treatment. Men should continue 6 months after their last cycle. Women should continue 12 months after their last cycle.

Breastfeeding

Ifosfamide passes into breastmilk therefore breastfeeding is contraindicated during ifosfamide treatment.

Emetogenic risk:

Moderate risk of sickness

Supportive treatments:

Thiamine 100mg THREE times each day for 14 days
Mesna 1600mg to be taken as directed when blood present in urine
Sodium Bicarbonate 500mg to be taken as directed if urine pH low
Domperidone 10mg THREE times each day when required

Extravasation risk:

Irritant

Patient's should contact the triage helpline if they are experiencing signs of extravasation.

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

Renal		
≥60	GFR	100%
40 – 59	GFR	70%
≤40	GFR	Not recommended Consider cyclophosphamide.

GFR to be calculated used Cockcroft and Gault formula

Hepatic		
Mild	Bilirubin >1.0-1.5 x ULN **OR** AST > ULN	No adjustment required
Moderate	Bilirubin 1.5-3 x ULN	No adjustment required
Severe	Bilirubin >3.0 x ULN	Not recommended Ifosfamide is metabolised to it's active form in the liver. Therefore, severe liver impairment can compromise cytotoxic activity.

According to Organ Dysfunction Working Group criteria:

Interactions:

Ifosfamide toxicity may be increased when used with any drug which can reduce renal function.

Cardiotoxicity may result when used in combination with cardiotoxic drugs.

CNS side effects can be additive when combined with any medication with CNS side effects.

Known enzyme inducers can increase activation of cytotoxic metabolites.

Known enzyme inhibitors reduce activation of ifosfamide potentially reducing cytotoxic activity. They may also effect metabolism and toxicity.

Treatment schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Ifosfamide + Mesna**	BSA 1.40m^2 to 1.60m^2 Ifosfamide 10,560mg + Mesna 10,600mg BSA 1.61m^2 to 1.80m^2 Ifosfamide 12,000mg + Mesna 10,000mg BSA 1.81m^2 to 2.00m^2 Ifosfamide 13,040mg + Mesna 9,000mg	IV	255ml sodium chloride 0.9% In LV1.5ml/ml PUMP Over 7 days
1 to 14	**Mesna ORAL**	1000mg/m^2 ONCE a day for 14 days	PO	ONCE a day
1 to 14	**Mesna ORAL**	1600mg to be taken as directed when blood present in urine	PO	When required
8	**Ifosfamide + Mesna**	BSA 1.40m^2 to 1.60m^2 Ifosfamide 10,560mg + Mesna 10,560mg BSA 1.61m^2 to 1.80m^2 Ifosfamide 12,000mg + Mesna 12,000mg BSA 1.81m^2 to 2.00m^2 Ifosfamide 13,040mg + Mesna 13,040mg	IV	255ml sodium chloride 0.9% In LV1.5ml/ml PUMP Over 7 days

Main toxicities:

Very common that side effects each occurring in at least 10% of patients include
- Haemorrhagic cystitis which potentially can lead to bladder fibrosis
- Neutropenia
- Alopecia,
- Mucositis,
- Nephrotoxicity,
- Nausea and vomiting

Side effects occurring in between 1% and 10% of patients include
- Hepatotoxicity
- Phlebitis

Less common serious side effects that occur with unknown frequency include
- Central neurotoxicity,
- Ovarian failure

Investigations and treatment plan:

		Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Ongoing
Informed Consent		X						
Medical Assessment		X	X	X	X	X	X	Every cycle
SACT Assessment (to include PS and toxicities)		X	X	X	X	X	X	Every cycle
FBC, U&E, LFTs		X	X	X	X	X	X	Every cycle
CrCl (Cockroft and Gault)		X	X	X	X	X	X	Every cycle
Corrected calcium Magnesium, Bicarbonate, Chloride		X	X	X	X	X	X	Every cycle
Urine PO_4, creatinine, osmolarity (early morning)			X		X		X	
Urine dipstick (for protein / blood			X	X	X	X	X	Every cycle
CT scan		X						As clinically indicated
ECG								If clinically indicated
Full observations		X	X	X	X	X	X	Every cycle
Weight recorded		X	X	X	X	X	X	Every cycle
Height recorded		X						
Pregnancy test		X						

Appropriate pregnancy measures are required for both during and after treatment. Men for 6 months after last treatment. Women for 12 months.

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

Parameter	Action
ANC 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
ANC < 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 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

Hepatic

Ifosfamide – note that ifosfamide is generally not recommended in severe hepatic impairment due to a lack of efficacy. In the reference trial patients were eligible for full dose treatment if bilirubin < 30micromol/L.[1]

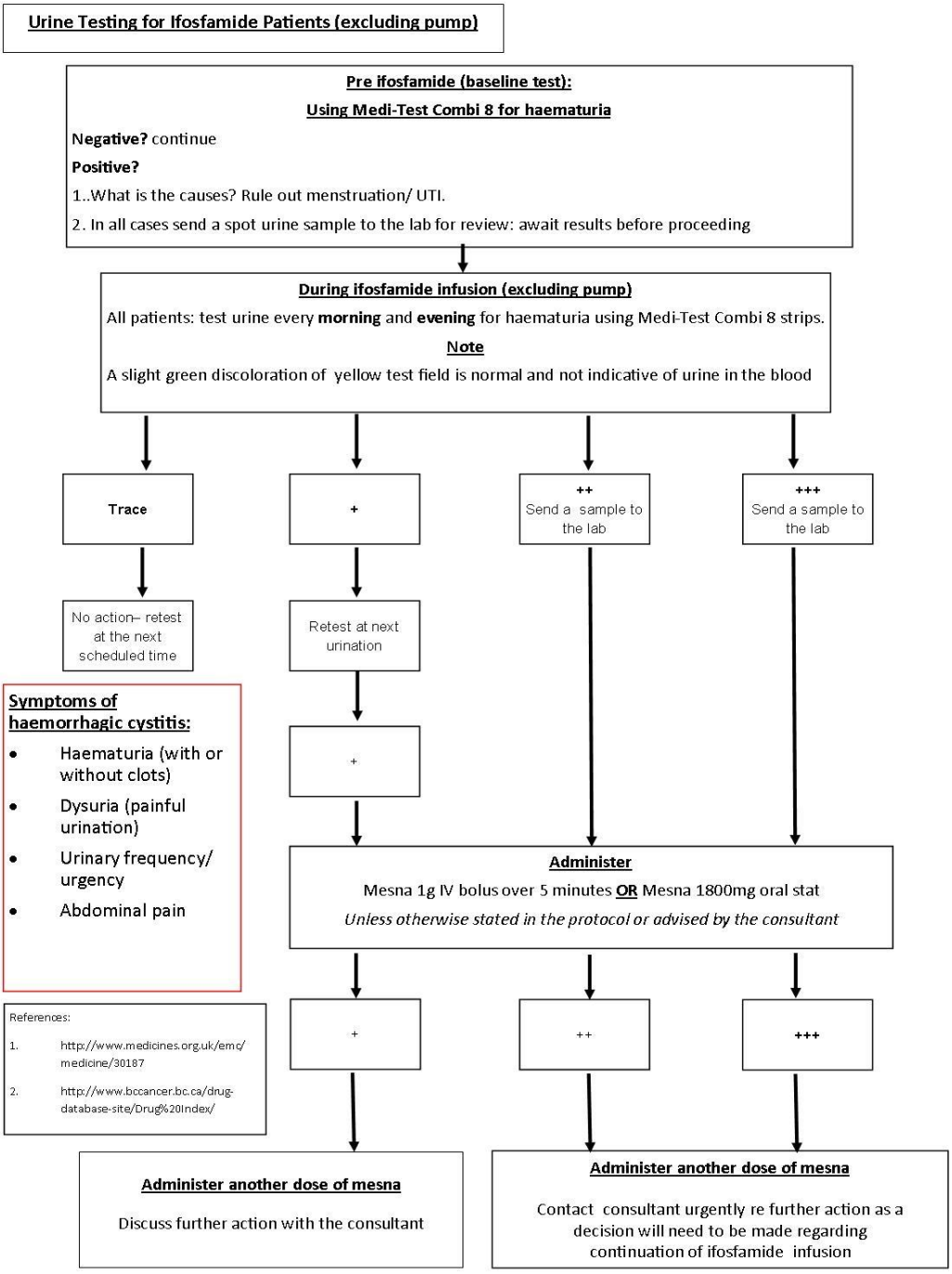
Neurotoxicity	**Central** Observe closely for signs of encephalopathy. This may present insidiously in a variety of ways but usually includes somnolence and confusion initially. Report any early signs to medical staff immediately Three risk factors may predispose to encephalopathy: renal impairment, low albumin, and large pelvic tumour mass. Note that most mild cases of encephalopathy will resolve spontaneously in 24 to 72 hours. 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) **Stop Ifosfamide infusion** consider the use of methylene blue (methylonium) 50mg IV infusion as follows: 50mg (5ml ampoule of 1% solution) every 4 hours, by IV slow bolus Patients who have had an episode of ifosfamide enduced encephalopathy in a previous cycle should be treated as follows: 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. 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 $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Non- Haematological toxicity:



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

Martin-Liberal et al, Clinical Activity and Tolerability of 14-Day Infusional Ifsofamide Schedule in Soft-Tissue Sarcoma. Sarcoma. 2013.

Supplement to: Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019; 20: e201–08.

Summary of Product Characteristics: Ifosfamide Injection 1g. Baxter Healthcare Ltd. Last review: 17/06/2016. Available via: https://www.medicines.org.uk/emc/product/1834 [Accessed 10/08/2021]

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
1.0	17/08/21	**Rob Challoner (Pharmacist)**	**First draft**