PROTOCOL

Systemic Anti Cancer Therapy Protocol

Ifosfamide + Mesna and Etoposide
Sarcoma

PROTOCOL REF: MPHAIFOETO
(Version No.1.2)

Approved for use in:

- 2nd line osteosarcoma
- 2nd line ewings sarcoma
- Other high grade bonesarcomas:

Dosage:

IE					
Drug	**Dosage**	**Days**			**Administration**
Etoposide	120mg/m^2	D1	D2	D3	Over 2 hours 1000ml Sodium Chloride 0.9%
Mesna	500mg/m^2	D1	D2	D3	Over 1 hour 500ml Sodium Chloride 0.9%
Ifosfamide + Mesna	3000mg/m^2 + 3000mg/m^2	D1	D2	D3	Over 4 hours 1000ml Sodium Chloride 0.9%
Mesna	3000mg/m^2	D1	D2	D3	Over 8 hours 1000ml Sodium Chloride 0.9%
Every 3 weeks for 6 cycles					

Administration & Counselling Points

Ifosfamide

Patients require measurement of their urine phosphate and creatinine prior to each cycle

The patient must fast overnight. The following morning, the patient should discard the first urine passed and then collect the second urine.

Patients require dipstick urine monitoring during treatment

Patients must report signs and symptoms of haemorhagic cystitis including blood in urine, pain on urination, abdominal pain, changes to urinary frequency or urgency.

Patients must report signs of encephalopathy including excessive sleepiness, disorientation, confusion or hallucination.

Administration: Ifosfamide

- Record patients weight at the same time each day as well as a strict fluid balance chart.
- If there is a positive 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)

Renal Function and Renal Tubular Reabsorption of Phosphate

A significant rise in serum creatinine must be discussed with a consultant even if CrCL >60mL/min discuss with consultant as ifosfamide may cause delayed impairment

Measure serum electrolytes and bicarbonate levels

Measure fasting urine phosphate and creatinine

Assess TmP/GFR (renal tubular resorption of phosphate) using calculator via citrix
http://clinicalapps.clatterbridgecc.nhs.uk/RTPR/

Use table below to evaluate renal toxicity

Toxicity grade	**GFR** mL/min/1.73m2	**TpCreat** mmol/L	**Bicarb*** mmol/L	**Action (apply worst grade)**
0 or 1	≥60	≥1.00	≥17.0	Continue ifosfamide at 100% dose
2	40-59	0.8-0.99	14-16.9	Ifosfamide 70% dose
3	≤40	≤0.80	≤14.0	Discuss with consultant potential switch to cyclophosphamide** dose 1500mg/m^2/d, day 1 only
*Consider potential causes for low HCO_3 before modifying ifosfamide dose e.g. infection				

Emetogenic risk:

Highly emetogenic.

Supportive treatments:

Metoclopramide 10mg oral tablets up to three times a day if required

Apreptitant prior to chemotherapy – 125mg on day 1 and 80mg on days 2 / 3

Dexamethasone 4mg TWICE daily for THREE days starting day after last IV chemotherapy

Filgrastim SC injection ONCE daily for SEVEN days starting day after last IV chemotherapy

Extravasation risk:

Etoposide- irritant
Ifosfamide- irritant

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

Dosing in renal and hepatic impairment:

Renal	Etoposide	**Creatinine clearance (mL/min)**	**Dose of etoposide**
		>50	100% of dose
		10-50	75% dose
		<15	contraindicated
	Ifosfamide	**Creatinine clearance (mL/min)**	**Dose of ifosfamide**
		≥60	100%
		40-59	70%
		<40	Clinical decision
		<15	Contraindicated

Hepatic	Etoposide	Etoposide is activated in the liver. Severe impairment may compromise efficacy of treatment. Bilirubin ≥ 50 µmol/L consider 50% of the dose, increase if tolerated	
	Ifosfamide	Mild	No adjustments required
		Moderate	
		Severe	Ifosfamide is activated in the liver. Severe impairment may compromise efficacy of treatment.

Mild	Bilirubin >1.0-1.5 x ULN **OR** AST > ULN
Moderate	Bilirubin 1.5-3 x ULN
Severe	Bilirubin >3.0 x ULN
As classified by Organ Dysfunction Working Group:	

Interactions:

Etoposide

- Concomitant phenytoin therapy is associated with increased etoposide clearance and reduced efficacy, and other enzyme-inducing antiepileptic therapy may be associated with increased etoposide clearance and reduced efficacy.
- Co-administration of antiepileptic drugs and etoposide can lead to decreased seizure control due to pharmacokinetic interactions between the drugs.
- Co-administration of warfarin and etoposide may result in elevated international normalized ratio.
- There is increased risk of fatal systemic vaccinal disease with the use of yellow fever vaccine. Live vaccines are contraindicated in immunosuppressed patients.

Ifosfamide

- Increased haematotoxicity and/or immunosuppression may result from a combined effect of ifosfamide and:
  - ACE inhibitors: ACE inhibitors can cause leukopenia.
  - Carboplatin
- Increased pulmonary toxicity may result from a combined effect of ifosfamide and, for example:
  - Amiodarone
  - G-CSF,
- Increased nephrotoxicity may result from a combined effect of ifosfamide and, for example:
  - Aciclovir
  - Aminoglycosides
- Inhibition of CYP 3A4 can also lead to increased formation of an ifosfamide metabolite associated with CNS and nephrotoxicity. CYP 3A4 inhibitors include:
  - Ketoconazole
  - Fluconazole
- Coumarin derivatives: Increased INR (increased international normalized ratio) has been reported in patients receiving ifosfamide and warfarin.
- Vaccines: The immunosuppressive effects of ifosfamide can be expected to reduce the response to vaccination. Use of live vaccines may lead to vaccine induced infection.
- Please refer to the SPC for more information.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant**	**125mg**	**PO**	30 minutes before chemotherapy
	Dexamethasone	**8mg**	**PO**	30 minutes before chemotherapy
	Ondansetron	**16mg**	**PO**	30 minutes before chemotherapy
	Etoposide	**120 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 120 minutes
	Mesna	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 60 minutes
	Ifosfamide +mesna	**3000mg/m^2 +3000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 4 hours
	Mesna	**3000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 8 hours
2	**Aprepitant**	**80mg**	**PO**	30 minutes before chemotherapy
	Dexamethasone	**8mg**	**PO**	30 minutes before chemotherapy
	Ondansetron	**16mg**	**PO**	30 minutes before chemotherapy
	Etoposide	**120 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 120 minutes
	Mesna	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 60 minutes
	Ifosfamide +mesna	**3000mg/m^2 +3000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 4 hours
	Mesna	**3000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 8 hours
3	**Aprepitant**	**80mg**	**PO**	30 minutes before chemotherapy
	Dexamethasone	**8mg**	**PO**	30 minutes before chemotherapy
	Ondansetron	**16mg**	**PO**	30 minutes before chemotherapy
	Etoposide	**120 mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 120 minutes
	Mesna	**500mg/m^2**	**IV**	Sodium Chloride 0.9% 500mL over 60 minutes
	Ifosfamide +mesna	**3000mg/m^2 +3000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 4 hours
	Mesna	**3000mg/m^2**	**IV**	Sodium Chloride 0.9% 1000mL over 8 hours

Main toxicities:

Etoposide

- Myelosuppression,
- Nausea & vomiting,
- Diarrhoea,
- Mucositis,
- Allergic reactions,
- Alopecia,
- Transient alterations in LFT
- Rarely peripheral neuropathy
- Hypertension

Ifosfamide

- Myleosuppression
- Decreased appetite
- Nausea/vomiting
- Hepatotoxicity
- Alopecia
- Renal dysfunction
- Haematuria
- Phlebitis
- Haemorrhagic cystitis

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Informed Consent	X							
Clinical Assessment	X					X**		As clinically indicated
SACT Assessment (to include PS and toxicities)	X	X	X	X	X	X	X	Every cycle
FBC	X		X	X	X	X	X	Every cycle
U&E & LFTs & Mg^2 Ca^{2+},Cl^-, HCO_3	X		X	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X		X	X	X	X	X	Every cycle
CT scan**	X							At the end of treatment and if clinically indicated
ECG								If clinically indicated
Fasting urine phosphate and creatinine		X	X	X	X	X	X	Every cycle
TmP/GFR		X	X	X	X	X	X	Every ifosfamide
Height recorded	X							If clinically indicated
Weight recorded	X	X	X	X	X	X	X	Every cycle
Urine dipstick for protein/ blood	X	X	X	X	X	X	X	See algorithm

Urine Dipstick testing for inpatients receiving Ifosfamide

Pre ifosfamide (baseline test):

Using medi-test combi 8 for haematuria
Negative? Continue
Positive?

1. What is the cause? Rule out menstruation/UTI
2. In all cases send a spot urine sample to the lab for review:

During ifosfamide infusion (excluding pump):

All patients: test urine every morning and evening for haematuria using Medi- test combi 8 strips

*A slight green discolouration of yellow test field is normal and not indicative of blood in the urine

Trace → No action-retest at the next scheduled time

\+ → Retest at next urination → + → **Administer** Mesna 1g IV bolus over 5 minutes or mesna 1800mg oral stat
Unless otherwise stated in the protocol or advised by the consultant

++ Send sample to the lab → **Administer** Mesna 1g IV bolus over 5 minutes or mesna 1800mg oral stat
Unless otherwise stated in the protocol or advised by the consultant

+++ Send a sample to the lab → **Administer** Mesna 1g IV bolus over 5 minutes or mesna 1800mg oral stat
Unless otherwise stated in the protocol or advised by the consultant

Symptoms of haemorrhagic cystitis:

- Haematuria (with or without clots)
- Dysuria(painful urination)
- Urinary frequency/urgency
- Abdominal pain

Retest at next urination

\+ → **Administer another dose of mesna**
Discuss further action with the consultant

++ → **Administer another dose of mesna**
Contact consultant urgently for further action as a decision will need to be made regarding continuation of ifosfamide infusion

+++ → **Administer another dose of mesna**
Contact consultant urgently for 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-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 100 x 10^9/L

Delay 1 week on day 1 if-

ANC ≤ 0.9 x 10^9/L	Plt ≤ 99 x 10^9/L

If platelets or ANC still below required levels for treatment at week 2, delay treatment again and patient will need assessed and chemotherapy dose reduction.

Parameter	Action
WBC or platelets recovery >6 days	Give 80% etoposide
Neutropenic sepsis grade 3/4	Give 80% etoposide

If there is further bone marrow toxicity then reduce etoposide dose by a further 20%. If necessary omit etoposide completely before reducing ifosfamide.

All dose reductions must be discussed with a consultant

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

GI/mucositis	If grade 3 / 4 give 80% dose of etoposide. If there is further GI toxicity then reduce etoposide by a further 20%. If necessary omit etoposide completely rather than reduce doses of the other drugs.
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** and give of Methylthioninium (Methylene Blue®) Methylthioninium 50mg in 100ml Glucose 5% over 10 mins repeated every 4 hours Secondary prophylaxis for subsequent cycles 30 mins prior to treatment give Methylthioninium 50mg in 100ml Glucose 5% over 10 mins Repeat every 6 hours for the 3 days of ifosfamide treatment. **For further information see trust policy entitled METHYLENE BLUE® FOR IFOSFAMIDE INDUCED ENCEPHALOPATHY (IIE)**

References:

Summary of Product Characteristics. *Ifofamide Injection 1g.* Baxter Healthcare Ltd. Electronic medicines compendium. [accessed on: 17/05/23] Last updated 04/04/2022

Summary of Product Characteristics*. Etoposide 20 mg/ml concentrate for solution for infusion.* Medac GmbH. Electronic medicines compendium. [accessed on: 17/05/23] Last updated 15/11/2022

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Goorin et al. Phase II/III trial of etoposide and high-dose ifosfamide in newly diagnosed metastatic osteosarcoma: a pediatric oncology group trial. J Clin Oncol. 2002 15;20

Circulation/Dissemination

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Version History

Revision	Date	Author name and designation	Summary of main changes
1.2	26/07/2023	**Anna Burke (pharmacist)** **Rob Challoner (pharmacist)**	**Renal and hepatic impairment, interactions, format, toxicities, supportive treatments** **Discussed with Dr Ali,** **Patient counselling section added, methylene blue section matched to methylblue protocol, info on renal resorption of phosphate updated, urine dipstick pathway minor corrections**