Systemic Anti Cancer Treatment Protocol

Doxorubicin and Ifosfamide
Sarcoma

PROTOCOL REF: MPHADOXIFO
(Version No: 1.0)

Approved for use in:

Soft tissue sarcoma

Dosage:

Drug	Dosage	Route	Frequency
Doxorubicin	20mg/m^2	IV	Days 1, 2 and 3 of cycle
Mesna	3g/m^2	IV	Days 1, 2 and 3 of cycle
Ifosfamide + Mesna	3g/m^2 + 3g/m^2	IV	Days 1, 2 and 3 of cycle
Mesna	3g/m^2	IV	Days 1, 2 and 3 of cycle

Repeat every 21 days for 4 to 6 cycles
For neo-adjuvant patients, usually 4 cycles

Supportive treatments:
Anti-emetic risk - high
Dexamethasone tablets, 4mg twice daily for 3 days
Domperidone 10mg oral tablets, up to 3 times a day or as required
Filgrastim to start on day 4 for 7 days, then repeat FBC, if neutrophils below 1.0 x 10^9/L then continue for further 7 days

Extravasation risk:

Doxorubicin: Vesicant – follow trust / network extravasation policy, specific treatment may apply
Ifosfamide: Irritant

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant 30 minutes prior to chemotherapy	125mg	PO	
1	Dexamethasone 30 minutes prior to chemotherapy	8mg	IV	Bolus injection
1	Ondansetron 30 minutes prior to chemotherapy	8mg	IV	Bolus injection
1	**Doxorubicin**	20mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing Sodium Chloride 0.9%
1	**Mesna**	3000mg/m^2	IV	In 500mL Sodium Chloride 0.9% over 60 minutes
1	**Ifosfamide** **+** **Mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL Sodium Chloride 0.9% over 4 hours
1	**Mesna**	3000mg/m^2	IV	1000ml Sodium Chloride 0.9% over 8 hours
2	Aprepitant	80mg	PO	24 hours after day 1 dose
2	Dexamethasone	8mg	IV	Bolus injection
2	Ondansetron	8mg	IV	Bolus injection
2	**Doxorubicin**	20mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing Sodium Chloride 0.9%
2	**Mesna**	3000mg/m^2	IV	In 500mL Sodium Chloride 0.9% over 60 minutes
2	**Ifosfamide + Mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL Sodium Chloride 0.9% over 4 hours
2	**Mesna**	3000mg/m^2	IV	1000ml Sodium Chloride 0.9% over 8 hours
3	Aprepitant	80mg	PO	24 hours after day 2 dose
3	Dexamethasone	8mg	IV	Bolus injection
3	Ondansetron	8mg	IV	Bolus injection
3	**Doxorubicin**	20mg/m^2	IV	Bolus injection over 10 minutes, with concurrent fast flowing Sodium Chloride 0.9%
3	**Mesna**	3000mg/m^2	IV	In 500mL Sodium Chloride 0.9% over 60 minutes
3	**Ifosfamide + Mesna**	3000mg/m^2 + 3000mg/m^2	IV	In 1000mL Sodium Chloride 0.9% over 4 hours
3	**Mesna**	3000mg/m^2	IV	1000ml Sodium Chloride 0.9% over 8 hours

Notes:

Doxorubicin

Maximum cumulative dose of doxorubicin: 450 to 550mg/m^2
Perform baseline MUGA if patient is considered at risk of significantly impaired cardiac contractility.
Use alternative regimen if cardiac ejection fraction < 50%
Repeat MUGA during treatment if there is any suspicion of cardiac impairment

Ifosfamide

Start the infusions at the same time each morning
Ensure adequate hydration and that fluids with Mesna are prescribed and administered.
Pre hydration with sodium chloride only needed on day 1
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 using Medi-Test Combi 8 pre-treatment and morning and evening during each cycle as per urine testing protocol (see algorithm)
Observe for insidious signs of encephalopathy, initially somnolence and confusion

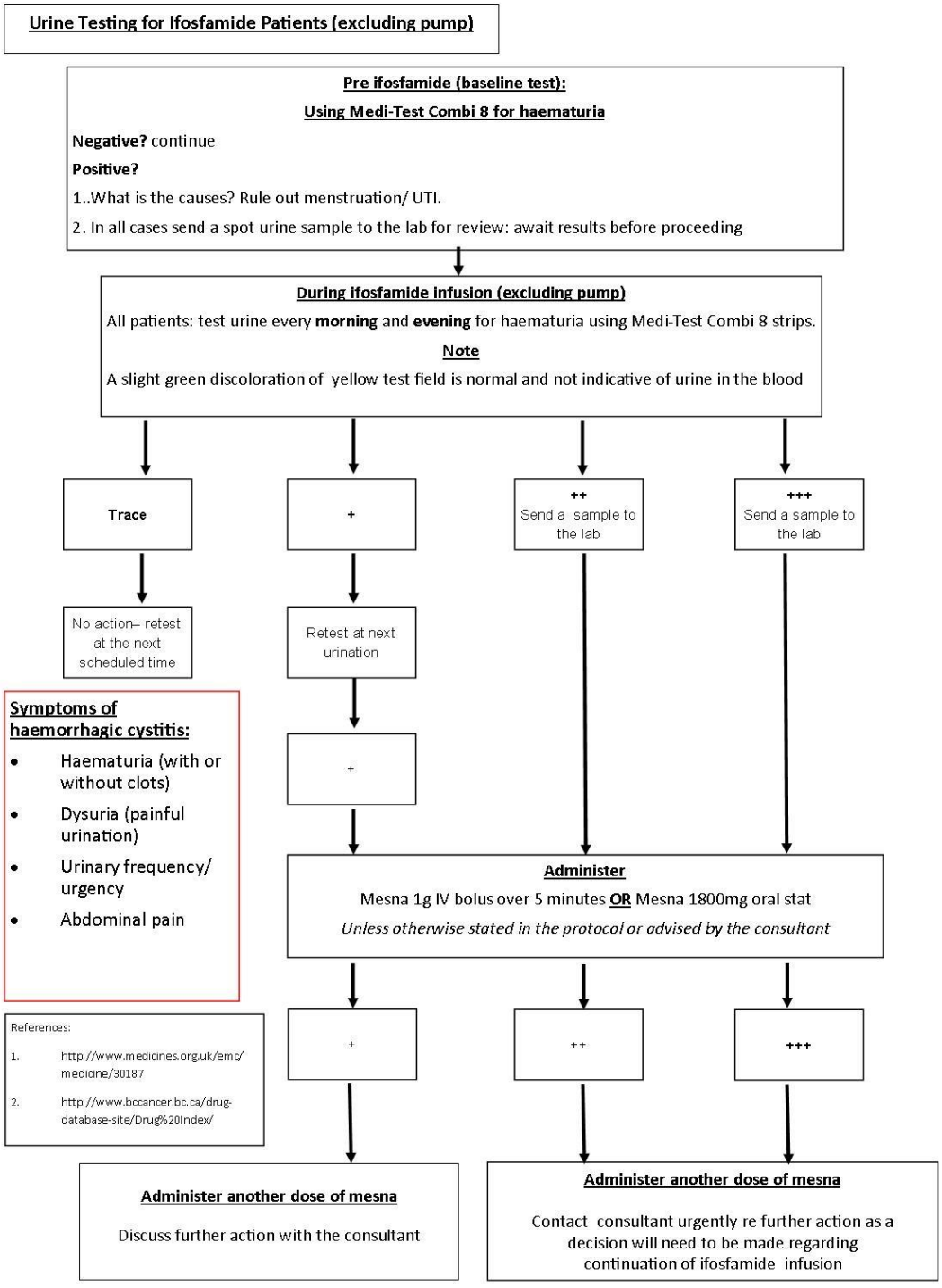
Main Toxicities:

Doxorubicin - Myelosuppression, alopecia, mucositis, cardiomyopathy (see notes and treatment plan), ovarian failure / infertility

Ifosfamide - 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	
Nursing Assessment	X	X	X	X	X	X	X	Every cycle
ECHO / ECG	X							If clinically indicated
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	
CT scan	X			X				As clinically indicated
Informed Consent	X							
Blood pressure measurement	X	X	X	X	X	X	X	Repeat if 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


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 on day 1 if:

ANC ≤ 0.9 x 10^9/L	Platelets ≤ 99 x 10^9/L

Discuss with consultant, and recheck every 2 to 3 days until recovered.

Non-haematological toxicity

Hepatic

Bilirubin (µmol/L)	Doxorubicin dose
20 to 50	50%
51 to 85	25%
Above 85	omit

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 less than 30micromol/L.

Renal

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

GFR (mL/min)	Ifosfamide dose
≥ 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/1.73m^2)	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 to 59	0.80 to 0.99	14.0 to 16.9	Ifosfamide 70% dose
Grade 3/4	≤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 ****Always discuss / check with consultant to confirm before substituting Cyclophosphamide 1500mg/m^2 dayc1 for ifosfamide.** If ifosfamide is stopped mid administration due to deteriorating renal function, continue with post hydration mesna until completed.	
Doxorubicin Cardiomyopathy	Perform baseline MUGA in any patient with suspected cardiac impairment. If cardiac ejection fraction < 50% discuss with consultant and consider an alternative regimen. Consider a lower maximum cumulative doxorubicin dose of 400mg/m^2 for any patient with cardiac dysfunction or that has been exposed to mediastinal radiation Note that cardiomyopathy may be delayed – if 20% reduction if LVEF after 300mg/m^2 then stop doxorubicin
Ifosfamide 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 of both drugs 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

EuroEwing 99 protocol

Collaboration SM-a. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: meta-analysis of individual data. Lancet 1997;350(9092):1647-54