Systemic Anti Cancer Treatment Protocol

Vincristine Ifosfamide Doxorubicin Etoposide (VIDE)
Sarcoma

PROTOCOL REF: MPHAVIDE
(Version No: 1.0)

Approved for use in:

Ewings sarcoma
Desmoplastic small round cell tumour

Cycles 1 to 6 of **VIDE** followed by cycles 7 to14 VAI (or VAC if renal toxicity is a concern, see separate protocols)

Dosage:

Schedule

VIDE x 6 > surgery (21 days after finish of cycle 6 or as soon as recovery occurs > VIA x 8 +/- radiotherapy

VIDE

Drug	Dosage	Route	Frequency
Vincristine	1.5 mg/m^2 (max 2mg)	IV	Day 1
Doxorubicin	20mg/m^2	IV	Days 1, 2 and 3 of cycle
Etoposide	150mg/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	See administration schedule		

Repeated every 21 days

Supportive treatments:
Anti-emetic risk – high

Aprepitant 125mg day 1, and 80mg days 2 and 3
Dexamethasone tablets, 4mg three times a day 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:

Vincristine – vesicant – follow trust /network policy, specific antidote may apply
Doxorubicin – vesicant – follow trust /network policy, specific antidote may apply
Etoposide – Irritant
Ifosfamide – Irritant

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Aprepitant	125mg	PO	30 minutes before chemotherapy
1	Dexamethasone	8mg	PO	30 minutes before chemotherapy
1	Ondansetron	16mg	PO	30 minutes before chemotherapy
1	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9% over 5 minutes
1	**Doxorubicin**	20mg/m^2	IV	Bolus injection over 10 mins, with concurrent fast flowing sodium chloride 0.9%
1	Mesna	1g/m^2	IV	500mL sodium chloride 0.9% over 1 hour
1	**Etoposide**	150mg/m^2	IV	1000mL sodium chloride 0.9% over 1 hour
1	**Ifosfamide** and mesna	1500mg/m^2 and 1500mg/m^2	IV	1000mL sodium chloride 0.9% over 8 hours
1	**Ifosfamide** and mesna	1500mg/m^2 and 1500mg/m^2	IV	1000mL sodium chloride 0.9% over 8 hours
2	Aprepitant	80mg	PO	24 hours after day 1 dose
2	Dexamethasone	8mg	PO	24 hours after day 1 dose
2	Ondansetron	16mg	PO	24 hours after day 1 dose
2	**Doxorubicin**	20mg/m^2	IV	Bolus injection over 10 mins (see day 1)
2	**Etoposide**	150mg/m^2	IV	1000mL sodium chloride 0.9% over 1 hour
2	**Ifosfamide** and mesna	1500mg/m^2 and 1500mg/m^2	IV	1000mL sodium chloride 0.9% over 8 hours
2	**Ifosfamide** and mesna	1500mg/m^2 and 1500mg/m^2	IV	1000mL sodium chloride 0.9% over 8 hours
3	Aprepitant	80mg	PO	24 hours after day 2 dose
3	Dexamethasone	8mg	PO	24 hours after day 2 dose
3	Ondansetron	16mg	PO	24 hours after day 2 dose
3	**Doxorubicin**	20mg/m^2	IV	Bolus injection over 10 minutes (see day 1)
3	**Etoposide**	150mg/m^2	IV	1000mL sodium chloride 0.9% over 1 hour
3	**Ifosfamide** and	1500mg/m^2 and	IV	1000mL sodium chloride 0.9%

	mesna	1500mg/m^2		over 8 hours
3	**Ifosfamide** and mesna	1500mg/m^2 and 1500mg/m^2	IV	1000mL sodium chloride 0.9% over 8 hours
3	Mesna	1500mg/m^2	IV	1000mL sodium chloride 0.9% over 2 hours
4 to 10	Filgrastim	30MU or 48MU	SC	Subcutaneous injection daily and repeat FBC

Give for 4 cycles and evaluate for definitive local therapy

Filgrastim dose:

For patients under 70kg: 30MU subcutaneous injection daily
For patients 70kg and above: 48MU subcutaneous injection daily

Evaluation	Action
Surgical resection likely	Proceed to cycles 5 and 6
Radiotherapy likely	Proceed to cycles 5 and 6
Radiotherapy prior to surgery	Proceed to cycles 5 and 6 but **omit doxorubicin if radiotherapy to be given concurrent with chemotherapy**

Primary bone sarcomas will have been discussed during the national MDT and therefore the outcomes from this must be taken into account when reviewing local plan.

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.
Substitute dactinomycin 1.5mg/m^2 if cardiac ejection fraction < 40%
Repeat MUGA during treatment if there is any suspicion of cardiac impairment

Ifosfamide

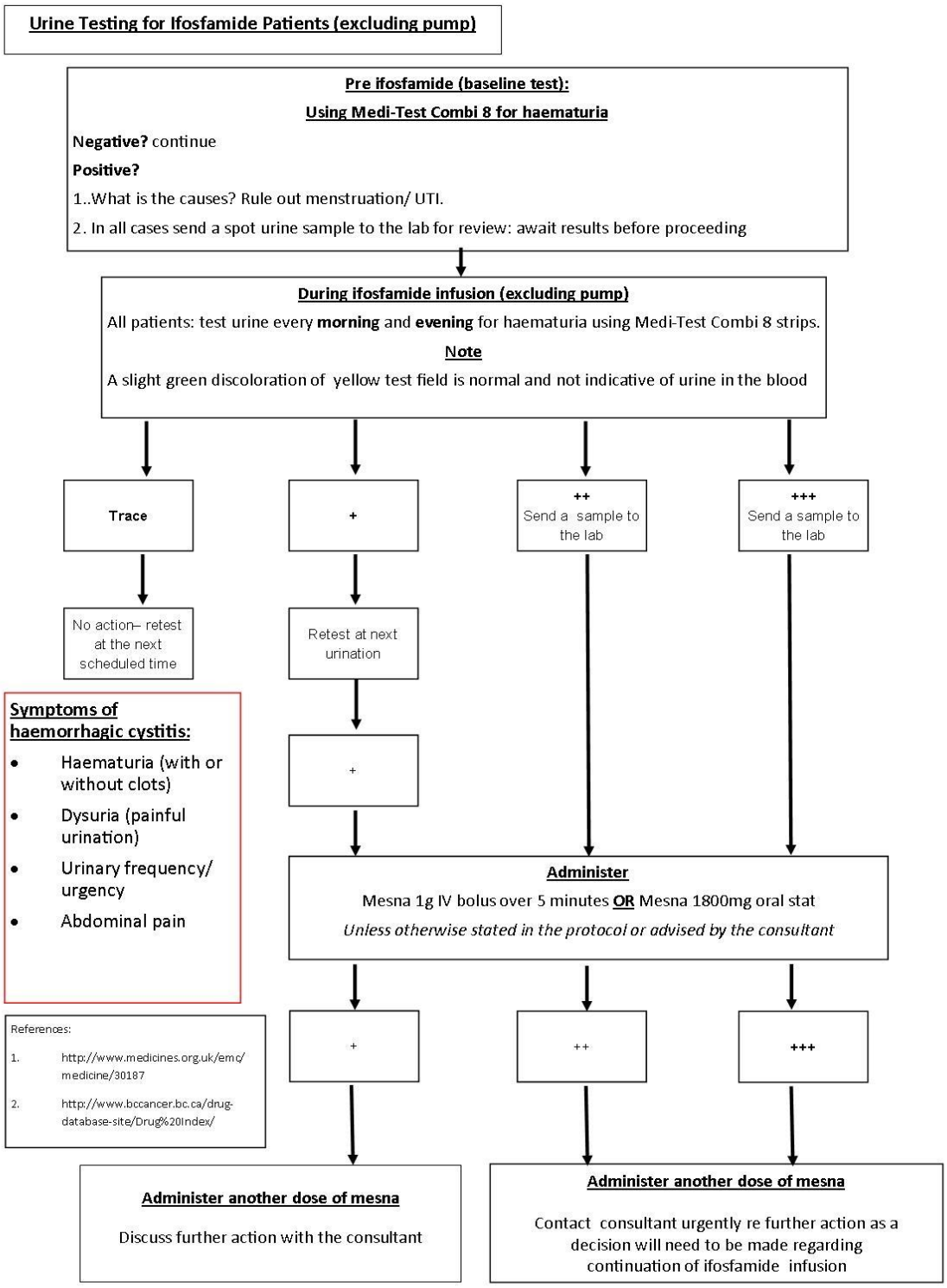
Ensure adequate hydration and that fluids with Mesna are prescribed and administered.
Record patients weight at the same time each day as well as a strict fluid balance chart. If there is a postitive fluid balance of 2litres or more, weight gain of > 2kg or symptoms of fluid overload give furosemide 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, mucositis, alopecia
Vincristine – neurotoxicity
Doxorubicin - ovarian failure / infertility
Ifosfamide – 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
MUGA/ECHO	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	X	X	X	X	X	X	X	
Tp/Ccrea		X	X	X	X	X	X	Every Ifosfamide
CT scan	X			X				As MDT plan
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	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:-

WCC ≥ 2.0 x 10^9/L	ANC ≥ 1.0 x 10^9/L	Platelets ≥ 80 x 10^9/L

If below these levels, discuss with consultant and repeat every 2 to 3 days until recovered.

Note that dose and time intensity is an important strategy for induction. Ensure that filgrastim is prescribed and given. If there is significant bone marrow toxicity reduce etoposide as shown rather than any of the other agents:

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 rather than reduce dose of any of the other drugs.

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.

Hepatic

Doxorubicin

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. See comments above about ifosfamide dose reductions

Etoposide – conflicting information exists for reductions with etoposide, use table below but discuss with oncologist if in doubt

Bilirubin (µmol/L)		AST/ALT (units/l)	Etoposide Dose
26 to 51	or	60 to 180	50%
Above 51	or	Above 180	Clinical decision

Renal

Measure serum creatinine each cycle and calculate CrCl using Cockroft

and Gault before each cycle of Ifosfamide.

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

Monitor renal function closely and if there is a significant rise in serum creatinine even if CrCl> 60 mL/min discuss with consultant as ifosfamide may cause delayed impairment.

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 to 59	0.80 to 0.99	14.0 to 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

****Always discuss / check with consultant to confirm before substituting Cyclophosphamide 1500mg/m^2 d1 for Ifosfamide.**

Cardiomyopathy	Perform baseline MUGA in any patient with suspected cardiac impairment. If cardiac ejection fraction < 50% discuss with consultant and consider an alternative regimen. Omit doxorubicin and substitute dactinomycin 1.5mg/m^2 if LVEF < 40% Repeat MUGA after next cycle and if cardiac function has recovered consider restarting doxorubicin. 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
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 **Other** Vincristine may also cause neurotoxicity autonomic and/ or peripheral. Discuss with consultant if any persistant neuropathy greater than grade 1.

References:

Juergens C, Weston C, Lewis I, Whelan J, Paulussen M, Oberlin O, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatric blood & cancer. 2006;47(1):22-9.

Thames Valley Cancer Network http://tvscn.nhs.uk/networks/cancer/cancer-topics/sarcoma/

Euro Ewing 2012 Euro Ewing 2012 - International Randomised Controlled Trial for the Treatment of Newly Diagnosed Ewing's Sarcoma Family of Tumours http://www.euroewing.eu/clinical-trials/ee2012-trial