Systemic Anti Cancer Treatment Protocol

Vincristine, Dactinomycin, Ifosfamide Sarcoma (VAI)

PROTOCOL REF: MPHAVINDAIF
(Version No: 1.1)

Approved for use in:

Ewings sarcoma – commencing after VIDE

Dosage:

Schedule

VIDE x 6 -> surgery (21 days after finish of cycle 6 or as soon as recovery occurs) ->

VAI x 8 +/- radiotherapy

VAI

Drug	Dosage	Route	Frequency
Vincristine	1.5mg/m^2 (max 2mg) day 1	IV	Every 21 days
Dactinomycin	0.75mg/m^2 days 1and 2 (max 1.5mg)	IV	Every 21 days
Ifosfamide +Mesna	3g/m^2 + 3g/m^2 days 1 and 2	IV	Every 21 days
Mesna	See Administration below		

Supportive treatments:

Anti-emetic risk – moderate / high

Dexamethasone tablets, 4mg twice daily for 3 days

Domperidone 10mg oral tablets, up to 3 times a day or as required

Filgrastim 30MU or 48MU subcutaneous injection daily for 7 days, repeat FBC and continue for further 7 days if neutrophil count has not recovered to 1.0 x 10^9/L

Extravasation risk:

Vincristine – vesicant – follow trust /network policy, specific antidote may apply

Dactinomycin – vesicant – follow trust /network policy, specific antidote may apply

Etoposide – irritant

Administration:

Day	Drug	Dosage	Route	Diluent and Rate
1	Dexamethasone 30 mins before chemotherapy	8mg	PO	
1	Ondansetron 30 mins before chemotherapy	16mg	PO	
1	**Vincristine**	1.5 mg/m^2 (max 2mg)	IV	In 50mL sodium chloride 0.9%
1	**Dactinomycin**	0.75mg/m^2 (max 1.5mg)	IV	In 100mL sodium chloride 0.9% over 30 minutes
1	**Mesna**	1000mg/m^2	IV	In 500mL sodium chloride 0.9% over 1 hour
1	**Ifosfamide + mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
1	**Ifosfamide + mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
1	**Mesna**	3000mg/m^2	IV	In 1000mL 0.9% sodium chloride over 4 hours
2	Dexamethasone	8mg	PO	24 hours after day 1 dose
2	Ondansetron	16mg	PO	24 hours after day 1 dose
2	**Dactinomycin**	0.75mg/m^2 (max 1.5mg)	IV	In 100mL sodium chloride 0.9% over 30 minutes Commence 24 hours after day 1 doses
2	**Mesna**	1000mg/m^2	IV	In 500mL sodium chloride 0.9% over 1 hour
2	**Ifosfamide + mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	**Ifosfamide + mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	**Mesna**	3000mg/m^2	IV	In 1000mL 0.9% sodium chloride over 4 hours

Give for 8 cycles

Notes:

Radiotherapy

This should start concurrently with cycle 7 of VIA

Omit dactinomycin during radiotherapy

If radiotherapy is required following surgery, delay until concurrent with cycle 8 VIA and omit Dactinomycin from concurrent cycles.

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 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:

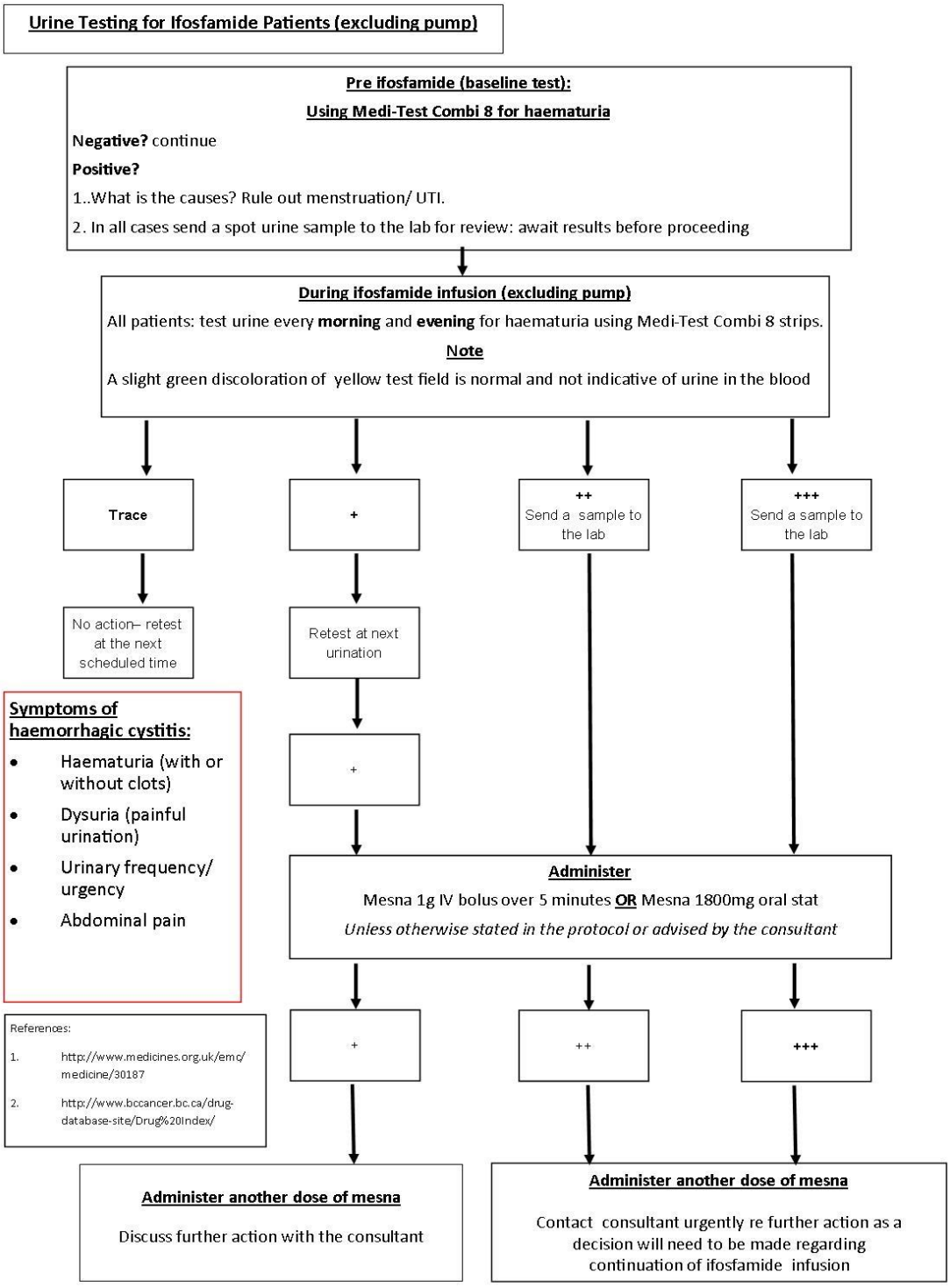
Vincristine – neurotoxicity

Dactinomycin - Myelosuppression, alopecia, mucositis, diarrhoea, liver changes (rare) ovarian failure / infertility

Ifosfamide – myelosuppression, mucositis, nephrotoxicity, central neurotoxicity, haemorrhagic cystitis leading to bladder fibrosis, ovarian failure

Investigations and treatment plan

	Pre	Cycle 7	Cycle 8	Cycle 9	Cycle 10	Cycle 11	Cycle 12	Cycle 13	Comments
Medical Assessment	X								
Nursing Assessment	X	X	X	X	X	X	X	X	Every cycle
ECHO/ECG	X								If clinically indicated
FBC	X	X	X	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	X	X	X	Every cycle
CrCl (Cockroft and Gault)	X	X	X	X	X	X	X	X	Every cycle
Ca^{2+}, Mg^{2+}, Cl^{-}, HCO_3	X	X	X	X	X	X	X	X	Every cycle
Urine PO_4, creatinine, osmolarity (early morning)	X		X		X		X	X	Every cycle
Serum HCO_3^{-} /total CO_2, PO_4		X	X	X	X	X	X	X	Every cycle
Tp/Ccrea		X	X	X	X	X	X	X	Every ifosfamide
CT scan	X			X					As clinically indicated
Informed Consent	X								
Blood pressure measurement	X	X	X	X	X	X	X	X	As clinically indicated
PS recorded	X	X	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	X	Every cycle
Urine dipstick for protein / blood	X	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

Note that in cases of significant bone marrow toxicity preference should be given to filgrastim support rather than dose reduction in order to maintain dose intensity. Do not reduce any doses or delay treatment without prior discussion with consultant

Proceed on day 1 if:-

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

Non-haematological toxicity

Renal	Monitor serum creatinine and calculate GFR using Cockroft and Gault before each cycle of Ifosfamide. 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 - 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

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

Hepatic	No specific guidance but consider dose reductions of dactinomycin in severe hepatic dysfunction
Gastric	Grade 3 or 4 mucositis or GI toxicity – reduce dactinomycin and ifosfamide to **80%** of original dose for first occurrence and **60%** of original dose for second occurrence

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 persistent 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/