Systemic Anti Cancer Treatment Protocol

VIP - Ifosfamide, Cisplatin and Etoposide

PROTOCOL REF: MPHAVIPGC
(Version No: 1.1)

Approved for use in:

Germ cell

Dosage:

Drug	Dosage	Route	Frequency
Etoposide	75mg/m^2 days 1 to 5	IV	Every 21 days
Cisplatin	20mg/m^2 days 1 to 5	IV	Every 21 days
Mesna	200mg/m^2 days 1 to 5	IV	Every 21 days
Ifosfamide +Mesna	1500mg/m^2 + 1500mg/m^2 days 1 to 5	IV	Every 21 days
Mesna	1200mg 1 to 5	Oral	Every 21 days

Supportive treatments:

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

Dexamethasone tablets, 4mg twice daily for 3 days

Filgrastim 30MU or 48MU subcutaneous injection daily for 7 days starting on day 6, repeat FBC and continue for further 7 days if neutrophil count has not recovered to 1.0 x 10^9/L

Extravasation risk:

Etoposide – Irritant

Cisplatin – Exfoliant

Ifosfamide - Neutral

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	**Etoposide**	**75mg/m^2**	IV	In 250 to 1000mL sodium chloride 0.9% over 60 minutes
1	**Cisplatin**	**20mg/m^2**	IV	1000mL 0.9% sodium chloride over 90 minutes
1	**Mesna**	**200mg/m^2**	IV	In 500mL sodium chloride 0.9% over 15 minutes
1	**Ifosfamide + Mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
1	**Mesna**	1200mg	PO	2 hours after completion of IV infusion
2	Dexamethasone 30 mins before chemotherapy	8mg	PO	
2	Ondansetron 30 mins before chemotherapy	16mg	PO	
2	**Etoposide**	75mg/m^2	IV	In 250 to 1000mL sodium chloride 0.9% over 60 minutes
2	**Cisplatin**	**20mg/m^2**	IV	1000mL 0.9% sodium chloride over 90 minutes
2	**Mesna**	**200mg/m^2**	IV	In 500mL sodium chloride 0.9% over 15 minutes
2	**Ifosfamide + Mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
2	**Mesna**	1200mg	PO	2 hours after completion of IV infusion
3	Dexamethasone 30 mins before chemotherapy	8mg	PO	
3	Ondansetron 30 mins before chemotherapy	16mg	PO	
3	**Etoposide**	75mg/m^2	IV	In 250 to 1000mL sodium chloride 0.9% over 60 minutes
3	**Cisplatin**	**20mg/m^2**	IV	1000mL 0.9% sodium chloride over 90 minutes
3	**Mesna**	**200mg/m^2**	IV	In 500mL sodium chloride 0.9% over 15 minutes
3	**Ifosfamide + Mesna**	1500mg/m^2	IV	In 1000mL sodium chloride

		+ 1500mg/m^2		0.9% over 4 hours
3	**Mesna**	1200mg	PO	2 hours after completion of IV infusion
4	Dexamethasone 30 mins before chemotherapy	8mg	PO	
4	Ondansetron 30 mins before chemotherapy	16mg	PO	
4	**Etoposide**	75mg/m^2	IV	In 250 to 1000mL sodium chloride 0.9% over 60 minutes
4	**Cisplatin**	**20mg/m^2**	IV	1000mL 0.9% sodium chloride over 90 minutes
4	**Mesna**	**200mg/m^2**	IV	In 500mL sodium chloride 0.9% over 15 minutes
4	**Ifosfamide + Mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
4	**Mesna**	1200mg	PO	2 hours after completion of IV infusion
5	Dexamethasone 30 mins before chemotherapy	8mg	PO	
5	Ondansetron 30 mins before chemotherapy	16mg	PO	
5	**Etoposide**	75mg/m^2	IV	In 250 to 1000mL sodium chloride 0.9% over 60 minutes
5	**Cisplatin**	**20mg/m^2**	IV	1000mL 0.9% sodium chloride over 90 minutes
5	**Mesna**	**200mg/m^2**	IV	In 500mL sodium chloride 0.9% over 15 minutes
5	**Ifosfamide + Mesna**	1500mg/m^2 + 1500mg/m^2	IV	In 1000mL sodium chloride 0.9% over 4 hours
5	**Mesna**	1200mg	PO	2 hours after completion of IV infusion

Cycle is repeated every 21 days for 4 cycles

Notes:

Cisplatin

Ensure adequate hydration pre and post cisplatin

Check and correct electrolytes, Mg^{2+}, Ca^{2+}, K^+ before starting cisplatin and check them regularly throughout treatment.

Encourage oral hydration throughout treatment e.g. one glass of water per hour.
Do not start Cisplatin infusion unless urine output is at least 100ml/hour.
Check patient's weight before and after each cisplatin infusion, maintain a strict fluid balance chart, ensure urine output is adequate. If necessary administer further 500ml 0.9% sodium chloride +/- furosemide 20 to 40mg po.
Give 20 to 40mg furosemide po if there is a positive fluid balance of 1.5 litres, weight gain of 2kg or symptoms of fluid overload.
The patient should be asked to drink 2 litres of fluid over 24 hours after the infusion and should be counselled refer to nurses if unable to do so for any reason.

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 (this also applies to cisplatin so only one dose is required)
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

Other

Ensure that primary prophylaxis with filgrastim on day 6 is prescribed and administered.
This should be 24 hours after the last chemotherapy
Ensure antiemetics are prescribed and given

Filgrastim dose:

For patients under 70kg: 300 micrograms subcutaneous injection daily
For patients 70kg and above: 480 micrograms subcutaneous injection daily

Main Toxicities:

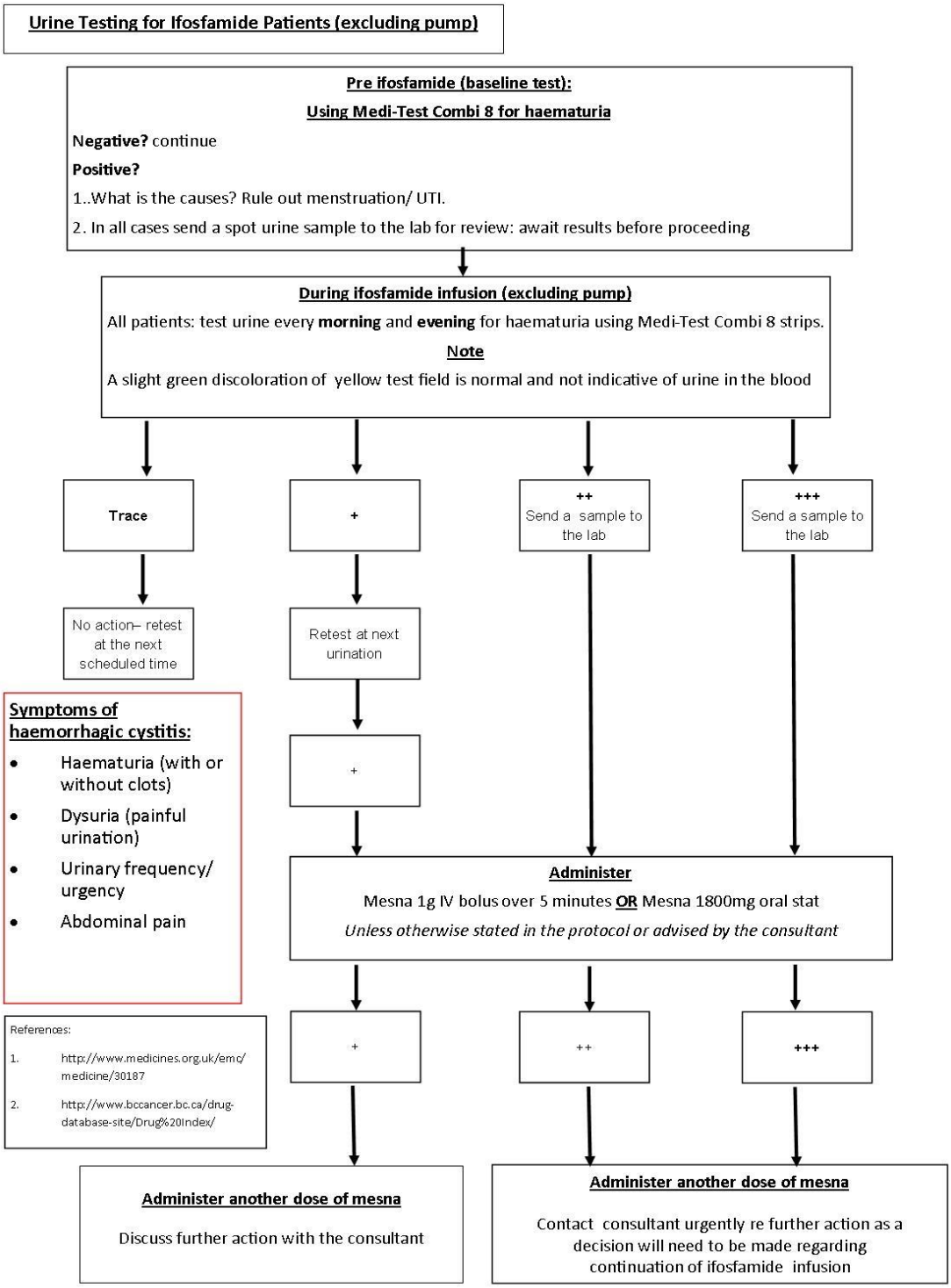
Etoposide – Nausea and vomiting, myelosuppression (thrombocytopenia, anaemia and neutropenia), Mucositis, oesophagitis and stomatitis occur infrequently. Alopecia, Anaphylactoid reactions. Hypotension may occur following an excessively rapid infusion of etoposide and may be reversed by slowing the infusion rate. Hypertension and/or flushing have also been reported. Blood pressure usually returns to normal within a few hours after cessation of the infusion. Bronchospasm. Peripheral neuropathy. Fatigue. Fever.

Cisplatin - leukopenia, thrombocytopenia and anaemia, anorexia, nausea, vomiting and diarrhea. Nephrotoxicity, urine output of 100 ml/hour or greater will help minimise this. Neuropathy. Ototoxicity.

Ifosfamide – myelosuppression normally followed by a reduction in the leukocyte count, mucositis, nephrotoxicity, and urotoxicity causing haemorrhagic cystitis leading to bladder fibrosis, ovarian failure, dose dependent central neurotoxicity leading to confusion, disorientation, drowsiness and psychosis.

Investigations:

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X		X		X	At end of treatment
Nursing Assessment	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	Day 1 of each cycle
Serum Creatinine	X	X	X	X	X	Every cycle
CrCl (Cockroft and Gault)	X	X	X	X	X	Every cycle
Tp/Ccrea		X	X	X	X	Every ifosfamide cycle
Ca^{2+}, Mg^{2+}, Cl^{-}, HCO_3	X	X	X	X	X	Repeat within the cycle if needed
LDH	X	X	X	X	X	Every cycle
AFP, βHCG	X	X	X	X	X	Every cycle
Urine PO_4, creatinine, osmolarity (early morning)		X	X	X	X	Every cycle
Serum HCO_3^- /total CO_2, PO_4		X	X	X	X	Every cycle
Blood pressure measurement	X	X	X	X	X	Every day
Informed Consent	X					First cycle
PS recorded	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	Every cycle
Urine dipstick for protein / blood	X	X	X	X	X	Every day, see algorithm below


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/
+
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+++
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:

Any delay in chemotherapy may be detrimental to outcomes

Do not delay chemotherapy or modify any doses without consultant approval

Haematological toxicity

Proceed on day 1 if:

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 100 x 10^9/L

Non-haematological toxicity

Renal

Cisplatin is eliminated primarily (>90%) in the urine and is itself nephrotoxic. If there is any significant renal toxicity discuss with consultant before proceeding.
Calculate CrCl before the start of treatment using Serum Creatinine and Cockroft and Gault. If the result is borderline consider EDTA clearance. Recalculate CrCl using Cockroft and Gault every cycle and consider EDTA if serum creatinine varies by >30% from baseline.

CrCl (mL/min)	Cisplatin dose
Above 60	100% dose
45 to 60	75% dose
Below 45	Do not give, discuss with consultant consider carboplatin
	Etoposide dose
Above 50	100% dose
15 to 50	75% dose
Below 15	50% dose

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

Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting advice about the need for dose adjustment with hepatic impairment. Use table below but discuss with consultant need for any adjustment

Bilirubin (micromol/L)	AST (units/L)	Etoposide Dose
26 to 51 OR	60 to 180	50% dose
Above 51 OR	Above 180	Clinical decision

GI toxicity

Cisplatin induced nausea and vomiting may be severe. Uncontrolled vomiting may exacerbate cisplatin induced fluid and electrolyte imbalance. Follow antiemetic policy rigorously and monitor fluids and electrolytes closely if severe vomiting occurs.
Note that electrolyte disturbance due to cisplatin may be a long term manifestation due to renal tubular dysfunction. Check electrolytes, longer term supplementation with magnesium, potassium or calcium may be required.

Grade 3 or 4 mucositis or GI toxicity – reduce ifosfamide to **80%** of original dose for first occurrence and **60%** of original dose for second occurrence

Acute reactions and fever

Cisplatin and Etoposide
Anaphylactic like reactions have been reported. These commonly include facial oedema, bronchoconstriction, tachycardia, hypotension. Follow trust anaphylactic policy.
Discuss next cycle with consultant before proceeding

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 induced 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

References:

Attili, V., Chandra, R., Anupama, G., Loknath, D., Bapsy, P., Dadhich, H. and Babu, G. (2007). Treatment outcome and cost-effectiveness analysis of two chemotherapeutic regimens (BEP vs. VIP) for poor-prognosis metastatic germ cell tumors. *Journal of Cancer Research and Therapeutics*, 3(3), p.150.

de Wit, R., Stoter, G., Sleijfer, D., Neijt, J., ten Bokkel Huinink, W., de Prijck, L., Collette, L. and Sylvester, R. (1998). Four cycles of BEP vs four cycles of VIP in patients with intermediate-prognosis metastatic testicular non-seminoma: a randomized study of the EORTC Genitourinary Tract Cancer Cooperative Group. *British Journal of Cancer*, 78(6), pp.828-832.