IPE

For use in patients with low and intermediate risk non-seminomatous germ cell tumours, who have a contra-indication to bleomycin

Drug/Dosage:	Ifosfamide	1000mg/m^2	IV	once daily for 5 days on Days 1 – 5
	Cisplatin	20mg/m^2	IV	once daily for 5 days on Days 1 - 5
	Etoposide	100mg/m^2	IV	once daily on Days 1, 3 and 5

G-CSF primary prophylaxis for 5 days, starting on Day 7

Administration: repeated daily for 5 days, and starting at the same time each day:

1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hours on Day 1, 2 and 4 of each cycle
Etoposide in 1 litre 0.9% sodium chloride over 2 hours on Days 1, 3 and 5 of each cycle
Mannitol 20% 100ml IV over 15 minutes
Cisplatin in 500ml 0.9% sodium chloride IV over 1 hour
1 litre 0.9% sodium chloride + 20mmol KCl + 10mmol $MgS0_4$ IV over 2 hrs
Mesna 200mg/m^2 IV slow bolus
Ifosfamide 1000mg/m^2} combined in 1000ml sodium chloride 0.9% IV
Mesna 1000mg/m^2} over 2 hours
Mesna 600mg/m^2 in 1 litre sodium chloride 0.9% IV over 8 hours

Frequency: 3 weekly cycle for 4 cycles

Main Toxicities: myelosuppression; CNS toxicity (see Comments); nephrotoxicity; haemorrhagic cystitis leading to bladder fibrosis (see Comments); ototoxicity; mucositis; neurotoxicity; alopecia; infertility

Anti emetics: Days 1 to 5: highly emetogenic, including aprepitant (note that oral dexamethasone x 3 days will start on Day 6)

Extravasation: non-vesicants

Regular Investigations:	FBC	Day 1
	U&Es and LFTs	Day 1
	Mg^{2+} and Ca^{2+}	Day 1
	AFP, βHCG, LDH	Day 1
	EDTA	prior to 1st cycle

Comments: Consider the use of allopurinol if patient has significantly bulky disease.

For patients on Cycle 1 whose EDTA is not yet available, it is acceptable to predict GFR using the Cockcroft and Gault formula if the patient has a stable serum creatinine. Cisplatin and ifosfamide doses should be adjusted if necessary once EDTA available. EDTA should only be repeated if the result is border-line at the start of treatment or if there is 30% change in serum creatinine.

Ensure careful review so that side effects such as peripheral neuropathy, hearing loss and pulmonary toxicity are detected early.

Reason for Update: new protocol	Approved by Consultant: Dr J Money-Kyrle
Version: 1	Approved by Lead Chemotherapy Nurse: P Deery
Supersedes: none	Date: 22.7.13
Prepared by: S Taylor	Checked by: C Tucker

Check electrolytes – additional potassium, calcium or magnesium may be required.

Weight should be recorded prior to and once daily throughout treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. If the urine output is inadequate, the patient should be assessed and urine output increased by administering 500ml sodium chloride 0.9% IV +/- furosemide 20 – 40mg. Furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload.

A urine sample should be tested twice daily (including once before the scheduled dose of ifosfamide is started) to look for signs of microscopic haematuria and, if seen, report to medical staff. (But note that the lowest level of blood detectable with some dipstick tests may be of little clinical significance)
Further mesna may be given as required if haemorrhagic cystitis is present eg. double the post-hydration mesna dose and give in 2L of fluid instead of 1L over the same time period in order to increase diuresis as well.
If haematuria is severe, ifosfamide should be discontinued until haematuria is resolved. **Discuss with Consultant**.

The patient should be encouraged to drink well. They should also be asked to drink 2 litres of fluid in the 24 hours following Day 5 of treatment. They should be told to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Post-hydration on Day 5 can be given orally to allow early discharge to patients considered suitable, as follows:
Mesna 400mg/m^2/dose po every 4 hours for a total of 3 doses, starting 1 hour prior to the end of ifosfamide infusion, along with 2 litres of water taken orally over 12 hours.

Note that if oral mesna is used, it is only 50% bioavailable and so doses should be adjusted accordingly. As mesna is essentially non-toxic, always round doses up rather than down – mesna is available as 400mg tablets.

Dose Modifications

Haematological Toxicity:

Dose modification and delays can compromise outcome and should be avoided. Patient **must not be delayed** without Consultant approval.

Neutrophils < 1.0 x 10^9/l or Platelets < 100 x 10^9/l	Delay for 3 days, and initiate G-CSF if appropriate. Repeat FBC and, if recovered, continue with full dose treatment. If FBC still low after 3 days, seek advice from Consultant.

Renal Impairment:

NB. Cisplatin and ifosfamide are both eliminated in the urine and nephrotoxic.

CrCl (ml/min)	Cisplatin Dose	Ifosfamide Dose
≥ 60	Give 100%	Give 100%
45 – 59	Give 75%	Give 70%
< 45	Treatment with this regimen is not recommended	

CrCl (ml/min)	Etoposide Dose
> 50	Give 100%
15 – 50	Give 75%
< 15	Give 50%

Hepatic Impairment: Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting information about dose reduction with hepatic impairment. Use the table below but, if in doubt, discuss with Consultant.

Bilirubin (μmol/l)		AST (units/l)	Etoposide Dose
26 – 51	**or**	60 - 180	Give 50% dose
> 51	**or**	> 180	Clinical decision

Ifosfamide is not recommended if bilirubin > 21μmol/l or if serum transaminases or ALP > 2.5 x ULN

Mucosal Toxicity: Severe mucositis will require delay of chemotherapy cycle to allow healing

Neurotoxicity: Seek further advice if patient reports symptoms indicative of oto- or neurotoxicity

Encephalopathy: Ifosfamide encephalopathy is an insidious condition (which can be fatal). Risk factors include renal impairment, low albumin and large pelvic tumour mass. It can present with a variety of symptoms, but usually somnolence and confusion feature strongly in the early stages, which must be promptly reported to a doctor.
Treatment suspension should be considered and is mandatory if Grade 3 or 4 neurotoxicity.
Methylene blue 50mg intravenously in 50-100ml sodium chloride 0.9% over 15 – 30 minutes, every 4 hours until symptoms resolve, can be used to attempt to reverse the encephalopathy. It should not be relied upon as a prophylactic measure, as it has not been rigorously assessed. Note that mesna has no ability to ameliorate CNS toxicity.

References : Nichols, C et al ; JCO 1998 ; 16 (4) : 1287 – 1293
De Wit, R et al ; Br J Cancer 1998 ; 78 (6) : 828 - 832
(but doses consistent with RMH practice)