IVE

Relapsed or refractory intermediate or high grade Non-Hodgkins Lymphoma, or relapsed Hodgkins disease, suitable for subsequent PBSCH and autograft
MDTs should carefully assess patient suitability with respect to tertiary centre criteria for high dose treatment, prior to starting salvage therapy

Drugs/Dosage/Administration:

Day	Drug	Dose	Fluid	Route	Frequency
1 only	Epirubicin	50mg/m^2	-	IV bolus via fast-running infusion of 0.9% Sodium Chloride	Single dose
1, 2 and 3 (3 doses)	Etoposide	200mg/m^2	In 1000ml 0.9% Sodium Chloride	IV over 2 hours	Once daily
1 only (loading dose pre ifosfamide)	Mesna	1800mg/m^2	In 100ml 0.9% Sodium Chloride	IV over 10 minutes	Single dose
1, 2 and 3 (3 doses)	Ifosfamide	3000mg/m^2	Mixed together in 1000ml 0.9% Sodium Chloride	IV over 22 hours	Once daily
	Mesna	3000mg/m^2			
1, 2 and 3 (3 doses)	-	-	1000ml Sodium Chloride 0.9%	IV over 22 hours	Once daily over the same time period as ifos/mesna
4 only	Mesna	5400mg/m^2	In 1000ml 0.9% Sodium Chloride	IV over 12 hours	Single dose

Other Drugs: Allopurinol 300mg po daily, ideally starting 24 hours before chemotherapy – review after 3 weeks
Fluconazole as prophylaxis throughout and until neutropenia resolved
G-CSF primary prophylaxis may be considered, according to ASCO guidelines and local practice

Frequency: Usually 2 cycles to achieve remission; maybe followed by a 3rd cycle for harvesting if remission achieved
Every 3 – 4 weeks, according to blood recovery

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

Anti-emetics: Highly emetogenic

Extravasation: Epirubicin is a vesicant

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Prepared by Oncology Pharmacist: S Taylor	Checked by Network Pharmacist: Jacky Turner

Regular Investigations:	FBC	alternate days until neutropenia or thrombocytopenia occur, then daily until recovery
	U&Es	D1, then twice weekly
	LFTs	D1, then twice weekly
	Mg^{2+} and Ca^{2+}	D1, then twice weekly
	Albumin	D1
	Cr^{51}-EDTA/24 hour urine	baseline
	MUGA scan/echo	see Comments
	Haematuria testing	until 24 hours after ifosfamide completed (see Comments)

Comments:

Maximum cumulative dose Epirubicin = 950mg/m^2 (remember to check and account for any previous anthracycline exposure)
A baseline MUGA scan/echo should be performed where the patient is considered at risk of having impaired cardiac function e.g. significant cardiac history, hypertension, obese, smoker, elderly, previous exposure to anthracyclines, previous thoracic radiotherapy. MUGA/echo should be repeated if there is suspicion of cardiac toxicity at any point during treatment, or if cumulative dose of epirubicin and any previous anthracyclines approaches maximum.

Weight should be recorded once daily and a strict fluid balance chart should be maintained. If there is a weight increase of 2kg, a positive fluid balance of 2 litres, or symptoms of fluid overload, furosemide 20-40mg po should be given.

Cr^{51}-EDTA / 24 hour urine collection should be repeated if there is a 30% change in serum creatinine.

Ifosfamide encephalopathy is an insidious condition (which can be fatal) that can present with a variety of symptoms, but usually somnolence and confusion feature strongly in the early stages. Three factors are known to predispose patients to this problem; renal impairment, low albumin and large pelvic tumour mass. If a patient has two of the three risk factors, future treatment should be reviewed by a Consultant.

Urine should be tested for signs of microscopic haematuria and, if seen, reported 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 present
eg. double the post-hydration mesna dose and give in 2 litres of fluid instead of 1 litre over the same time period in order to increase diuresis as well. If haematuria is severe, dose modification or discontinuation of ifosfamide may be required. Discuss with Consultant.

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.

Dose Modifications **Important note** - because this regimen is used in the context of salvage therapy for potentially curable patients, any dose reductions *must be confirmed by the treating Consultant and/or tertiary centre.* The dose modifications outlined below are not mandatory but are intended to guide discussion and decision making.

Haematological Toxicity: Proceed with treatment only if neutrophils > 1.0 x 10^9/L and platelets > 75 x 10^9/L
Delay in count recovery after treatment should be managed according to local protocols/practice

Renal Impairment:

GFR (ml/min)	Ifosfamide Dose
> 60	Give 100%
40 - 59	Give 70%
< 40	Not advised

CrCl (ml/min)	Etoposide Dose
60	Give 85%
45	Give 80%
30	Give 75%

Hepatic Impairment:

Bilirubin (µmol/l)	Epirubicin Dose
24 – 51	Give 50% dose
>51	Give 25% dose

Ifosfamide is not recommended if bilirubin > 17µmol/l or if serum transaminases or ALP > 2.5 x ULN

Creatinine clearance is the strongest predictor of etoposide clearance. There is conflicting information about dose reduction with hepatic impairment. Use the table below, but discuss with Consultant before any dose reductions are made.

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

Encephalopathy: Somnolence and confusion are early stage symptoms, 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, 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.

Patient Information: CancerBACUP leaflets for Ifosfamide, Etoposide and Epirubicin

References: JS de Bono, EJ Fitzsimmons & DJ Dunlop; Ann Oncol (1999); 10 (S3): 381

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