[R]-ICE

[NOTE: There is also a modified RICE protocol which can be administered in ambulatory setting for patient(s) meeting criteria. Refer to local Ambulatory Care Operational Policy]

INDICATION

LYMPHOMA [ICD-10 codes: C.81, C.83, C.85]

- Licensed / NHSE funded
  - ✓ Relapsed or refractory lymphoma
  - ✓ Primary or secondary CNS lymphoma as part of frontline treatment

[Omit rituximab if CD20-negative]

TREATMENT INTENT

Curative

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - CT scan (neck, chest, abdomen and pelvis), and/or PET-CT, presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests - FBC, ESR, DAT, U&Es, LDH, urate, calcium, magnesium, creatinine, LFTs, glucose, Igs, β_2 microglobulin, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, CMV, VZV, HIV 1+2 after consent.
4. See 'Guidelines for the use of blood components in adult haematology' for individual patient requirements. **NB: All patients who are receiving priming chemotherapy for PBSC collection require irradiated blood products 7 days prior to harvest until harvest complete. Please send a "group and save" sample to blood transfusion and inform patient and transfusion laboratory +/- referring DGH need for requirements.** Ensure irradiated blood product card is attached to patient's notes and copy given to patient.
5. Urine pregnancy test - before cycle 1 of each chemotherapy course for women of child bearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
6. ECG +/- Echo - *if clinically indicated*.
7. Record performance status (WHO/ECOG).
8. Record height and weight.
9. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent prior to treatment.
10. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Hydration - *in patients with bulky disease* pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. For patients at high risk of tumour lysis, refer to the tumour lysis protocol.
12. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. 24 hours urine collection for Creatinine clearance (patients in trial had CrCl >60 mL/min).
14. Fluid balance chart essential for all patients.

15. Venous access should be assessed well in advance of collection. Make every effort not to use antecubital fossa veins in the run up to harvest. Apheresis line to be inserted if poor antecubital veins (Hickman line should be inserted prior to first cycle).
16. Liaise with BMT nurse co-ordinator for timing of harvest and possible transplant slot.
17. Ensure the peripheral stem cell harvest / final donor clearance form (form FRM3721/1) is sent within 30 days of scheduled harvest date, via nhs.net mail to NHSBT STS, to confirm eligibility for PBSCH.
18. Treatment should be agreed in the relevant MDT.
19. This chemotherapy regimen is usually delivered during an inpatient stay but can be used in ambulatory setting for patient(s) meeting criteria. Refer to local Ambulatory Care Operational Policy.
20. Infective agent screen. Peripheral blood stem cells for autologous transplant are cryopreserved in liquid nitrogen. In order to eliminate the risk of transmitting infective agents during the storage of marrow, virology testing is mandatory within 30 days of the harvesting procedure and results must be known before priming. Bottles and consent form provided by NHSBT Oxford. Please send to the stem cell laboratory Oxford. Address provided on consent form.

DRUG REGIMEN

Day(s)	Drug	Dose	Route	Administration details
1	Pre-medications 30 min before rituximab[a]	Paracetamol 1g Chlorphenamine 10mg Hydrocortisone 100mg	PO PO IV bolus	
1	**RITUXIMAB[a]**	375mg/m^2	IV infusion	In 500mL sodium chloride 0.9% ***[Refer to Protocol Care Plans - Rituximab infusion rates, max 400mg/hour]***[b]
1, 2, 3	**ETOPOSIDE**	100mg/m^2	IV infusion	In 250-1000mL sodium chloride 0.9% (concentration<0.4mg/mL) over 1 hour [lumen 2][c]
2	**CARBOPLATIN**	(GFR[d]+25) x AUC 5 (max. 800mg)	IV infusion	In 500mL glucose 0.5% over 30 minutes [lumen 1] ***[Check urine output]***[e]
2 (T=0)	MESNA	1000mg/m^2	IV bolus	
2 (T=0)	**IFOSFAMIDE + MESNA**	[h]5000mg/m^2 + 5000mg/m^2	IV infusion	in 3000mL sodium chloride 0.9% over 24 hours [lumen 1] *[split in 3 x 1000mL (8-hourly) bags due to ifosfamide/mesna stability]* ***[Dipstick all urine for blood]***[f]
3 (T=24)	Sodium chloride	0.9%	IV infusion	1000mL over 12 hours [lumen 1] starting immediately after the end of ifosfamide/mesna infusion
3 (T=24, 26, 30)	MESNA	2000mg/m^2	PO	3 doses in total, administered immediately after ifosfamide + mesna infusion, then 2 hours and 6 hours after the end of infusion
6-13	GCSF	Depending on priming or non-priming indication[g]	SC	Refer to local hospital policy [OUH Filgrastim guideline]
CYCLE FREQUENCY: every 3 weeks (or as soon after haematological recovery)				
DURATION: 3 – 6 cycles				

[a] Omit if CD20 negative
[b] If appropriate criteria met, consider rapid rate for rituximab infusion. Refer to OUH guideline [Link]
[c] On day 2, etoposide [lumen 2] runs concurrently with ifosfamide [lumen 1]
[d] GFR (Glomerular filtration rate) = CrCl (creatinine clearance) [ml/min] calculated using Wright formula
[e] Check urine output: If >100 mL/hour, continue to ifosfamide; If <60-100 mL/hr, administer 200 mL mannitol 20% over 30 minutes
[f] Dipstick all urine for blood. See OUH guidance if positive for blood [Link]
[g] G-CSF should be discontinued after completion of stem cell harvesting. Pegfilgrastim must not be used
[h]Maximum ifosfamide dose given as 24-hourly infusion (using 3 x 8-hourly ifosfamide bags) = 9600mg (national dose banding)

RESTAGING

After second cycle to assess response with CT or PET-CT. Partial or complete response, proceed to third cycle and high dose therapy. Less than partial response, discuss at lymphoma MDT.

HARVESTING (if used for priming)

- Stem cell collection performed days 13 and 14.
- Aim to collect minimum of 3.0 x 10^6 with target of 4.0 x 10^6 CD34-positive cells/kg

DOSE MODIFICATIONS

Haematological toxicity

Proceed with full dose if neutrophils ≥1 x 10^9/L, platelets ≥50 x 10^9/L. If under threshold, please discuss with consultant responsible for treatment.

Renal dose adjustments- Based on GFR/ CrCl (mL/min)

ETOPOSIDE	≥50 mL/min	Full dose- 100%
	15 – 49 mL/min	75% dose
	<15 mL/min	Clinical decision. Further dose reduction usually required, consider overall regimen feasibility.
	Haemodialysis (HD)	Consider overall regimen feasibility. Not dialysed, 75% dose
CARBOPLATIN	Dose using Calvert equation and discuss with consultant to decide target AUC. Contraindicated if CrCl <20 mL/min, dosing in haemodialysis should be discussed with pharmacist.	
IFOSFAMIDE*	≥60 mL/min	Full dose- 100%
	40 – 59 ml/min	70% dose
	<40 mL/min	Clinical decision, discuss with consultant May consider cyclophosphamide as alternative
	Haemodialysis (HD)	Consider overall regimen feasibility, not routinely recommended. Limited data is available.

*Dosing recommendations as per prior practice. A decision has been made not to align with Lancet[4] renal dosing recommendations due to significant increased risk of neural toxicity.

Haemodialysis recommendations are not directly correlated to adjustments required in other forms of dialysis (e.g. peritoneal dialysis) or renal replacement therapy (RRT). Seek specialist advice.

Hepatic dose adjustments

ETOPOSIDE	Bilirubin <50 umol/L, **AND** normal albumin **AND** normal renal function	No dose adjustment
	Bilirubin ≥50 umol/L **OR** decreased albumin levels	Consider 50% dosing, increase if tolerated well.
	Patients with raised bilirubin and/or decreased albumin may have an increase in free etoposide and hence greater myelosuppression.	
CARBOPLATIN	Routine dose adjustment not required – discuss with consultant if concerns.	
IFOSFAMIDE	Mild or Moderate (Child Pugh A or B)	Discuss with consultant. No need for dose adjustment is expected.
	Severe (Child Pugh C)	Not recommended, due to risk of reduced efficacy.
	Note ifosfamide is protein bound. Patients presenting with significant hypoalbuminemia may be at greater risk of neurotoxicity, assess neurotoxicity risk (Appendix 1)	

INVESTIGATIONS

- Clinical examination, documentation of adverse events and disease progression.
- Twice weekly FBC, U&Es, creatinine, LFTs, Mg^{2+} and Ca^{2+} - ensure Hb > 10g/dL, platelets > 20 x 10^9/L, and Mg and Ca are within normal limits prior to harvest, arranging replacements as necessary and updating NHSBT STS with current plan.

POTENTIALLY HAZARDOUS INTERACTIONS WITH OTHER DRUGS

Ifosfamide possibly enhances effect of warfarin (may increase the INR).

CONCURRENT MEDICATION

Allopurinol (first cycle after relapse)	300 mg od for 7 days starting 24 hours before first dose of chemo
Proton pump inhibitor (PPI)	Daily for the duration of treatment (as per local formulary)
Fluconazole	50 mg daily for the duration of treatment
Aciclovir	200 mg three times a day for duration of treatment and for 3 months after completion
GCSF	As per local policy from D6 to D13
Mesna	2000 mg/m^2 PO immediately after and at 2 hours and 6 hours after the **END** of ifosfamide infusion (3 doses in total) If patient cannot tolerate oral administration, oral mesna can be replaced with either: 1) a single **MESNA** 3000mg/m2 IV infusion over 12 hours in 1000mL sodium chloride 0.9%, **OR** 2) **MESNA** 1000 mg/m^2 in 100 mL sodium chloride 0.9% IV infusion over 30 minutes at t = 28hr, 32hr & 36hr for fluid restricted patient.

EMETIC RISK

Day 1: Low
Day 2: High
Day 3: Moderate

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- Ifosfamide may irritate bladder mucosa. Patients should be encouraged to drink a minimum of three litres of fluid per 24 hours.
- Encephalopathy.
- Carboplatin- nephrotoxicity, ototoxicity – assess patient for tinnitus or hearing abnormalities.
- Ifosfamide- neurotoxicity (see below), nephrotoxicity, haemorrhagic cystitis, hypokalaemia, hypocalcaemia, hypophosphataemia, alopecia, nausea, vomiting, decreased appetite.
- Etoposide- alopecia, appetite decreased, arrhythmia, constipation, diarrhoea, hepatotoxicity, mucositis, nausea, vomiting.
- Rituximab – severe cytokine release syndrome is characterized by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. Hepatitis B reactivation – see pathway for treatment and management of HBV positive patient.

IFOSFAMIDE INDUCED HAEMORRHAGIC CYSTITIS: Managing positive urine dip for blood

Test Result	Action
Trace	Re-test
+	Re-test; if positive on more than one consecutive test give additional IV bolus mesna. Check fluids and any concurrent mesna is running correctly or oral dose has been taken.
++ / +++	Double dose of any concurrently running IV mesna. Ambulatory patients should be considered for admission for IV bolus and/or infusional mesna until haematuria resolved. Repeated ++ / +++ result, or evidence of macroscopic haematuria should prompt pause and review of current treatment.

Recommended bolus dose: Mesna intravenous 600mg/m2 or a fixed dose of 1 gram in 250ml sodium chloride 0.9% over 30mins.

Patients needing bolus mesna should have their infusional mesna or oral doses doubled for all subsequent chemotherapy treatments. Ambulatory patients should be carefully risk assessed for admission in future cycles.

IFOSFAMIDE-INDUCED ENCEPHALOPATHY AND/OR NEUROTOXICITY

Methylene blue (methylthioninium chloride (Proveblue®)) should be given for prophylaxis and treatment of ifosfamide-induced encephalopathy. This is an unlicensed indication.

Prophylactic methylene blue use should be considered in patients at high risk of toxicity, refer to nomogram (Appendix 1) to aid assessment of risk status.

Use of methylene blue is contra-indicated in:

- Glucose-6-phosphate dehydrogenase (G6PD) deficiency
- Patients with nitrite-induced methaemoglobinaemia during treatment of cyanide poisoning
- Patients with methaemoglobinaemia due to chlorate poisoning
- Deficiency in NADPH (nicotinamide adenine dinucleotide phosphate) reductase.

Symptoms[§]	**Intervention**
Mild (Grade 1) somnolence, agitation, tremor, delirium or extrapyramidal symptoms	• Monitor neurological status (standard neuro observations). • Limit rate of ifosfamide infusion, maximum rate 1g/m2/hour.
Moderate (Grade 2) somnolence, agitation, tremor, delirium or extrapyramidal symptoms	• Strict monitoring of neurological status. • **Start methylene blue** • **If worsening toxicity- STOP ifosfamide infusion,** continue mesna, and ensure 4-hourly methylene blue administration. • Continue treatment until all signs of neurotoxicity have resolved.
Severe (Grade 3) somnolence, agitation, tremor, delirium or extrapyramidal symptoms ***OR* any other severe neurological event** e.g., toxic psychosis, seizures, coma	• Strict monitoring of neurological status. Consider ICU • **Immediately discontinue ifosfamide.** Mesna treatment should continue to protect the bladder. • **Start methylene blue, or increase to maximum dose** • Continue treatment until all signs of neurotoxicity have resolved. • **Avoid further treatment with ifosfamide**

[§]Grading as per CTCAE 5.0, list of possible symptoms is not exhaustive

Commence treatment with the following recommended dosing:

Intravenous (IV) administration	**Treatment of moderate symptoms or prophylactic use:** 50mg IV TDS (8 hourly) in 50 – 100 ml glucose 5% as slow IV bolus over minimum 5 minutes. **Treatment of moderate-severe symptoms:** Increase frequency of dosing to **4-hourly.**
Oral (PO) administration	**For prophylactic use only** Methylene blue 50mg TDS (6 – 8 hourly) PO. Use injection for oral administration. Dilute one ampoule in 100ml water before administration to minimize GI effects. Drink through a draw to avoid staining teeth. 53-97% oral absorption.

Patients resuming treatment after previous toxicity should receive prophylactic dosing with all further cycles of ifosfamide.

EXTRAVASATION RISK

Rituximab: Neutral
Ifosfamide: Neutral
Carboplatin: Irritant
Etoposide: Irritant

TREATMENT RELATED MORTALITY

<1%

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REVIEW

Name	Revision	Date	Version	Review date
NSSG Lymphoma Group	Annual Protocol Meeting	May 2018	1.6	
Cheuk-kie Jackie Cheung (Pharmacist)	Ambulatory care information added, Day 3 IV mesna replaced with PO mesna, adverse effect section updated. Carboplatin infusion time changed to 30min.	Nov 2019	1.7	May 2020
NSSG Lymphoma Group	Annual Protocol Review	Aug 2020	1.8	May 2021
Sara Castro & Donna Constantine, Haematology Pharmacists, NSSG Lymphoma Group,	Update of dose adjustment guidance. Addition of neurotoxicity nomogram and treatment guidance. Correction to methylene blue dilution and administration. Annual Protocol Review	May 2021	1.9	May 2023
Graham Collins, Haematology Consultant, Natalia Czub, Haematology Pharmacist NSSG Lymphoma Group	Indication, drug regimen updated. Ifosfamide with mesna 24-hourly infusion delivered using 3 subsequent bags started immediately after last one ending. Annual Protocol Review	July 2022	2.0	July 2023

APPENDIX 1- Ifosfamide neural toxicity nomogram

The following nomogram can be used, to aid decision making, regarding the use of prophylactic methylene blue. Pre-treatment albumin and creatinine should be measured, and a ruler placed across the two values. Use the relevant scale depending on the presence of pelvic disease.

Consider where:

- Previous ifosfamide induced neurotoxicity
- Serum creatinine >150 µmol/L
- Serum albumin <30 g/L

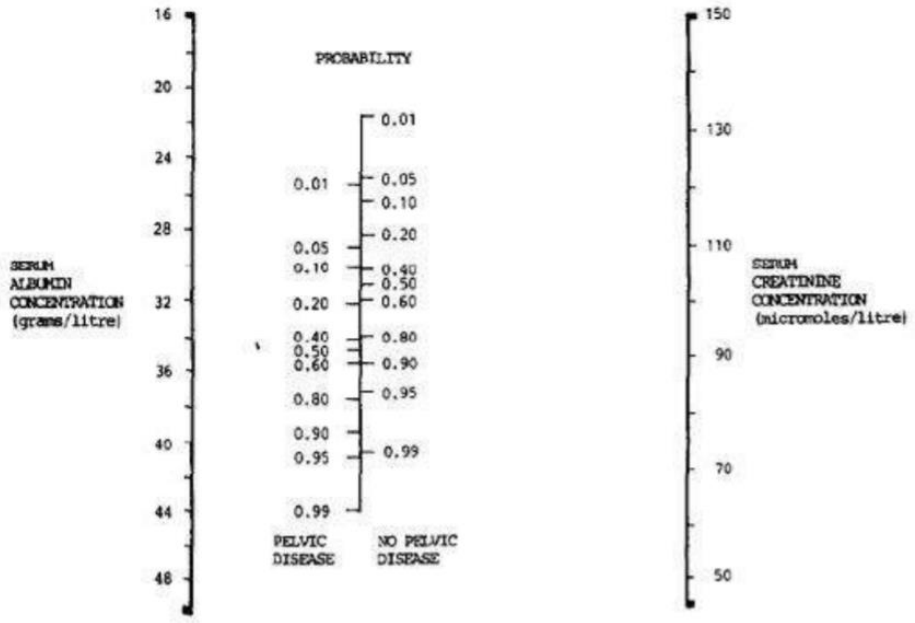

Fig. 1. Nomogram to determine probability of not developing grade 3–4 clinical CNS toxicity with ifosfamide/mesna 36 hr infusion. The probability that a patient will **NOT** *develop severe CNS toxicity falls on the intersection of a straight line joining their serum albumin and serum creatinine concentrations on the appropriate pelvic disease scale.*

Source:
Meanwell, C., Blake, A., Kelly, K., Honigsberger, L. and Blackledge, G. (1986). Prediction of Ifosfamide/Mesna associated encephalopathy. Eur J Cancer Clin Oncol 22 (7), pp. 815-819.