R-ICE

INDICATION

Salvage treatment for relapsed or refractory lymphoma. 
Omit rituximab if CD20-negative and consider omitting rituximab if relapsed rapidly following rituximab-containing regimen.

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, β2 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 G+S sample to blood transfusion and inform the patient, transfusion +/- 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 new 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), height and weight.
8. 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.
9. 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.
10. 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.
11. Consider dental assessment / Advise dental check is carried out by patient’s own dental practitioner before treatment starts.
12. 24 hours urine collection for Creatinine clearance (patients in trial had CrCl >60 mL/min).
13. Fluid balance chart essential for all patients.
14. 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 (line should be inserted prior to first cycle).
15. Liaise with BMT nurse co-ordinator for timing of harvest and possible transplant slot.
16. 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.
17. Treatment should be agreed in the relevant MDT.
18. 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.

**NB:** 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 1**

Pre med - Paracetamol 1 g PO, chlorphenamine 10 mg IV, hydrocortisone 100 mg IV. Give 30 minutes before rituximab.

**RITUXIMAB** 375 mg/m² IV infusion daily in 500 mL sodium chloride 0.9%.

**Day 1, 2 & 3**

**ETOPOSIDE** 100 mg/m² IV infusion in 500-1000 mL sodium chloride 0.9% over 1 hour daily. (On day 3, etoposide runs concurrently with ifosfamide (lumen 2)).

**Day 2**

**CARBOPLATIN (AUC=5)** IV infusion in 500 mL glucose 5% over 30 minutes (Max dose 800 mg) [Dose (mg) = AUC 5 x (creatinine clearance + 25). Using Wright formula]. Check urine output:
- If >100 mL/hr, continue to ifosfamide.
- If <60-100 mL/hr, administer 200 mL mannitol 20% over 30 minutes.

**Day 2**

**MESNA** 1000 mg/m² IV bolus over 5 min prior to giving ifosfamide infusion.

**Day 2 (t=0-24)**

**IFOSFAMIDE** 5000 mg/m² (max = 10 g) + **MESNA** 5000 mg/m²

[Ifosfamide & Mesna combined in 1 litre sodium chloride 0.9% IV infusion over 24 hrs (lumen 1) run concurrently with 2 litres sodium chloride 0.9% IV infusion over 24 hours (lumen 2)].

**Day 3**

**MESNA** 2000 mg/m² PO immediately after ifosfamide infusion, and at 2 hours and 6 hours after the END of ifosfamide infusion (3 doses in total). See concurrent medication section if patient is unable to tolerate oral administration.

**When used for priming:**

**Days 6 to 13**

Daily G-CSF as per local policy. Continue until mobilisation completed. G-CSF should be discontinued after completion of stem cell harvesting. (Pegfilgrastim must NOT be used)

**When not used for priming:**

**Days 6 to 13**

Daily G-CSF as per local policy.

Dipstick all urine for blood (ifosfamide induced haemorrhagic cystitis). Consider increasing hydration and an additional bolus of mesna alongside vigilant monitoring.
IFOSFAMIDE-INDUCED ENCEPHALOPATHY

Refer to nomogram to assess risk.

**CYCLE FREQUENCY**

Repeat every three weeks or as soon as there is sufficient haematological recovery for a total of 3-4 cycles.

**RESTAGING**

After second course to assess response with CT or PET-CT. Partial or complete response, proceed to third course 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 $2.0 \times 10^6$ with target of $4.0 \times 10^6$ CD34-positive cells/kg

**DOSE MODIFICATIONS**

**Haematological toxicity**

Proceed with full dose if Hb >10 g/dL, neutrophils $\geq 1 \times 10^9$/L, platelets $\geq 50 \times 10^9$/L. If not, please discuss with consultant responsible for treatment.

**Etoposide:**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl (mL/min)</td>
<td>Bilirubin 26-51 micromol/L OR AST 60-180 u/L</td>
</tr>
<tr>
<td>$&gt;50$</td>
<td>Bilirubin $&gt;51$ micromol/L OR AST $&gt;180$ u/L</td>
</tr>
<tr>
<td>15-50</td>
<td>75%</td>
</tr>
<tr>
<td>$&lt;15$</td>
<td>50%</td>
</tr>
</tbody>
</table>

Subsequent doses should be based on clinical response.

Patients with raised bilirubin and/or decreased albumin may have an increase in free etoposide and hence greater myelosuppression.

**Carboplatin:**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose using Calvert equation: Dose = AUC (25 + GFR) Contraindicated if CrCl $&lt;20$ mL/min. Discuss with consultant.</td>
<td></td>
</tr>
</tbody>
</table>

This is a controlled document and therefore must not be changed or photocopied
Ifosfamide:

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment - discuss with consultant</th>
</tr>
</thead>
<tbody>
<tr>
<td>GFR &gt;60 mL/min 100% dose</td>
<td>SPC recommendations: Not recommended in patients with a Bilirubin &gt;17 micromol/L or serum transaminases or ALP &gt;2.5 x ULN. Clinical decision.</td>
</tr>
<tr>
<td>GFR 40-59 mL/min 70% dose</td>
<td></td>
</tr>
<tr>
<td>GFR &lt;40 mL/min clinical decision.</td>
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</tbody>
</table>

INVESTIGATIONS

- Clinical examination, documentation of adverse events and disease progression.
- Twice weekly FBC, U&Es, creatinine, LFTs, Mg++ and Ca++ - 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.

CONCURRENT MEDICATION

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allopurinol (first cycle after relapse)</td>
<td>300 mg od for 7 days starting 24 hours before first dose of chemo</td>
</tr>
<tr>
<td>Proton Pump Inhibitor or H₂ antagonist</td>
<td>Daily for the duration of treatment</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>50 mg daily for the duration of treatment</td>
</tr>
<tr>
<td>Aciclovir</td>
<td>200 mg three times a day for duration of treatment and for 3 months after completion</td>
</tr>
<tr>
<td>GCSF</td>
<td>As per local policy from D6 to D13.</td>
</tr>
<tr>
<td>Mesna</td>
<td>2000 mg/m² PO immediately after and at 2 hours and 6 hours after the END of ifosfamide infusion (3 doses in total)</td>
</tr>
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</table>

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/m² 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.
- Etoposide, Epirubicin- alopecia, deranged LFTs
- Rituximab - severe cytokine release syndrome is characterised 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-related neurotoxicity: Ifosfamide must be discontinued immediately. Methylene blue can be given as treatment of ifosfamide-induced encephalopathy. Refer to nomogram to assess risk.

**Dose**: 50 mg TDS IV or orally. NB: 50 mg = 5 mL of 1% solution.

**IV**: Administer 50 mg in 50 to 100 mL sodium chloride 0.9% or glucose 5%, over 15 to 30 mins.

**Orally**: Use injection for oral administration. Dilute one ampoule in 100 mL water before taking orally to minimise GI effects. Drink through a straw to avoid staining teeth. 53-97% oral absorption. Dexamethasone may cause steroid related SE – monitor BMs.

EXTRAVASATION RISK

- Rituximab: neutral
- Ifosfamide: neutral
- Carboplatin: irritant
- Etoposide: irritant

TREATMENT RELATED MORTALITY

<1%
REFERENCES


<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
</tr>
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<tbody>
<tr>
<td>NSSG Lymphoma Group</td>
<td>Annual Protocol Meeting</td>
<td>May 2018</td>
<td>1.6</td>
<td></td>
</tr>
<tr>
<td>Cheuk-kie Jackie Cheung (Pharmacist)</td>
<td>Ambulatory care information added, Day 3 IV mesna replaced with PO mesna, adverse effect section updated. Carboplatin infusion time changed to 30minutes.</td>
<td>Nov 2019</td>
<td>1.7</td>
<td>May 2020</td>
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