R-ESHAP

[Rituximab, Etoposide, Methylprednisolone, Cytarabine, Cisplatin]

INDICATIONS

Licensed*/NHSE funded: **LYMPHOMA** [ICD-10 codes: C81-85]

- Relapsed or refractory Hodgkin lymphoma
- Relapsed or refractory non-Hodgkin lymphoma

Omit rituximab for CD20 negative lymphoma

*Unlicensed indications (off-label use): cytarabine (Hodgkin lymphoma), methylprednisolone and cisplatin (lymphoma) – ensure compliance with treating Trust's governance framework.

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease - contrast enhanced CT scan (neck, chest, abdomen and pelvis), and/or PET-CT scan, presence or absence of B symptoms, clinical extent of disease. Bone marrow trephine if clinically indicated in non-Hodgkin lymphoma.
3. Blood tests - FBC, ESR, U&Es, LDH, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, HbA1c, Igs, β_2 microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV, HTLV-1, glucose 6-phosphate dehydrogenase (G6PD) when indicated [H.8]; group and save.
4. Assess **glycaemic control** as steroids in this regimen can increase the risk of hyperglycaemia. All patients should have a baseline HbA1c and venous plasma glucose checked prior to commencing treatment, followed by venous plasma glucose checked at each cycle and antidiabetic medications managed according to local policies and the UK Chemotherapy Board and Joint British Diabetes Societies for Inpatient Care [JBDS-IP] guideline.
5. **Irradiated blood products if used for Hodgkin lymphoma and/or for priming for stem cell collection.** Refer to [Guidelines for the use of blood components in adult haematology]. Ensure the requirement for irradiated blood products for future transfusions has been flagged to the transfusion laboratory. Please send a **"group and save"** sample to blood transfusion and inform patient +/- referring district general hospital (DGH) about the need for irradiated bloods requirements**.** Ensure irradiation card is given to the patient.
6. Urine pregnancy test - before cycle 1 of each chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
7. ECG +/- ECHO - if clinically indicated.
8. Record performance status [ECOG].
9. Record vital signs, height and weight.
10. Consent and counselling - 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.
11. 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.
12. Assess and document tumour lysis risk as part of pre-assessment. Hydration – in patients with bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Refer to the Tumour Lysis Syndrome in Adults protocol [H.8].

13. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
14. This regimen can be delivered during an inpatient stay or **can be used in ambulatory setting for patient(s) meeting the criteria**. Refer to local **Ambulatory Care Operational Policy.**
15. Treatment should be agreed in the relevant MDT.

When R-ESHAP regimen is used for priming and harvesting:

1. Liaise with BMT nurse co-ordinator for timing of harvest and possible transplant slot.
2. **Stem cell collection should be performed on days 15 & 16 of the cycle.**
3. **Aim to collect 4.0x10⁶ CD34-positive cells/kg [minimum of 2.0x10⁶ CD34-positive cells/kg].**
4. Venous access should be assessed well in advance of collection. Every effort should be made not to use antecubital fossa veins in the run up to harvest. If good antecubital fossa veins, insert power PICC. Apheresis line to be inserted if poor antecubital veins.
5. Ensure the peripheral stem cell harvest / final donor clearance form (FRM3721) is sent within 30 days of scheduled harvest date to NHSBT to confirm eligibility for PBSCH.
6. **Infective agent screen.** Peripheral blood stem cells for autologous transplant are cryopreserved in liquid nitrogen. 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 NHSBT stem cell laboratory in Oxford. Address is provided on the consent form.

DRUG REGIMEN

Day(s)	Drug	Dose	Route	Administration details
1–5	**METHYLPREDNISOLONE**	**500 mg**	IV or PO	Day 1 if rituximab given: at least 30 minutes prior to rituximab infusion IV infusion (sodium succinate): in 100 mL sodium chloride 0.9% over 15 minutes PO: Available as 100mg tablets
1	Chlorphenamine Paracetamol	10 mg 1000 mg	IV PO	Pre-medications: 30 minutes before rituximab
1	**RITUXIMAB***	**375 mg/m²**	IV	In 500mL sodium chloride 0.9% [Refer to [Nursing Care Plans: Rituximab infusion rates], max. rate 400mg/hour]. Patients should be observed for 30 minutes before the start of other infusions. If first dose is well tolerated, consider a rapid infusion rituximab rate from cycle(s) 2 onwards.
1–4	**ETOPOSIDE**	**40 mg/m²/day**	IV	in 250-500 mL sodium chloride 0.9% over 1 hour [concentration 0.2–0.4 mg/mL]
1–4	Pre-hydration Sodium chloride 0.9%	500mL	IV	over 30 minutes, before cisplatin infusion on day 1, then once daily on days 2–4
1–4	**CISPLATIN**	**25 mg/m²/day**	IV	**For inpatients**: 25mg/m² in 1L sodium chloride 0.9% over 22 hours on days 1-4 (total dose = 100 mg/m² over 4 days) **For outpatients**: 100mg/m² in 250mL sodium chloride 0.9% (CADD cassette) or 192mL sodium chloride 0.9% (elastomeric pump) as continuous infusion over 4 days (96 hours)**
1–4	Post-hydration Oral fluids	500mL	PO	**For inpatients:** Patients required to drink at least 500mL post each cisplatin infusion **For outpatients:** Patients required to drink at least 2-3 L/day on cisplatin days
5	**CYTARABINE**	**2000 mg/m²**	IV	in 250 mL sodium chloride 0.9% over 3 hours
CYCLE FREQUENCY: 21-28 days, depending on blood counts recovery				
DURATION: 3 cycles (including priming), otherwise up to 6 cycles				

*__Rituximab__ – consider in all CD20 positive patients. Depending on the chemotherapy day units' capacity, rituximab may also be given on day 5, instead of day 1, at discretion of individual Trusts.

**__For outpatients – Cisplatin dose > 185mg__ (i.e., max. dose in one 192mL elastomeric pump): Consider giving remainder of the dose in the second elastomeric pump on day 5, at the Consultant discretion. NB. Cytarabine should be moved to day 6, to avoid administration with cisplatin on the same day due to increased risk of cytotoxic adverse reactions.

Cisplatin Hydration – Monitoring during chemotherapy

- Monitor urine output at regular intervals throughout chemotherapy
- At the end of IV fluids, weigh the patient and review fluid input and output
- Re-weigh the patient – if they have gained > 2 kg or clinically appear fluid overloaded, they should be prescribed furosemide 40mg orally and urine output monitored for a further 30 minutes.
- Furosemide usage may be appropriate in patients predisposed to cardiac failure from hydration. Discuss with medical team if there are any concerns. Except for patients receiving doses of cisplatin exceeding 60 mg/m^2, whose urine secretion is less than 1 L/24 hours, no forced diuresis with loop diuretics should be applied in view of possible damage to the kidney tract and ototoxicity.

CONCURRENT MEDICATIONS

TLS prophylaxis		Hydration + allopurinol 300mg OD (reduce dose in renal impairment) for 7 days or consider rasburicase if high risk TLS [Cycle 1]. Refer for full details to the Tumour Lysis Syndrome in Adults protocol [H.8].
Antiviral prophylaxis		Aciclovir 200mg TDS during treatment and for 3 months after completion
Antifungal prophylaxis		Fluconazole 50mg OD for the duration of treatment
PJP prophylaxis		Co-trimoxazole 480mg three times a week on Mon/Wed/Fri for duration of treatment and at least 3 months after completion. Pentamidine can be considered for patients who are intolerant or allergic to co-trimoxazole.
Gastric protection		Omeprazole 20mg OD on days 1–5
Cytarabine-induced conjunctivitis prophylaxis		Steroid eye drops, as per local formulary, for example, prednisolone 0.5% (Minims) or dexamethasone 0.1%. One drop to each eye QDS from day 3 and continue for 5 days after last cytarabine dose. In the event of conjunctivitis, consider increasing the frequency to 2-hourly until resolution of symptoms. Consult with Ophthalmologists as appropriate.
G-CSF	**Non-priming cycles**	Filgrastim **0.5 MU/kg/day**, on days 6–12
	Priming cycle	Filgrastim **1.0 MU/kg/day**, on days 6–15 or continue until mobilisation completed. G-CSF should be discontinued after completion of stem cell harvesting (Peg-filgrastim must NOT be used).
Anti-emetics Days 1-5: Moderate risk		▪ Ondansetron on days 1-5: 8mg BD ▪ Metoclopramide on days 1-8: 10-20mg TDS. For breakthrough nausea or vomiting: 10-20mg TDS when required. For alternative options, refer to [TVCA Anti-emetic guideline].
Vitamin D supplement*		If required: Vitamin D < 50 nmol/L: replace as per local formulary
Bone protection*		Refer to the Bone Protection in Lymphoma guidance [L.132]

(*) indicates optional concurrent medications

CONTRAINDICATIONS

Refer to individual medications Summary of Product Characteristics (SmPCs)

INVESTIGATIONS

- Before each cycle: FBC, U&Es, magnesium, creatinine, LFTs, glucose, bone profile
- Before harvest: ensure Hb > 100 g/L, platelets > 20 x 10^9/L, magnesium and adjusted calcium are within normal limits, arranging replacements as necessary and updating NHSBT with the current plan.

RESTAGING

After 2 cycles with CT or PET-CT.

TREATMENT MODIFICATIONS

All dose modifications should be discussed with the Consultant.

Haematolological toxicities:

Prior to each cycle: ensure neutrophil count ≥ 1 x 10^9/L and platelet count ≥ 75 x 10^9/L

Non-haematological toxicities:

Ototoxicity: Consider omitting the platinum agent.

	Renal impairment	**Hepatic impairment**
Etoposide	GFR > 50 mL/min: 100% dose GFR 15-50 mL/min: 75% dose, increase if tolerated GFR < 15 mL/min: no data, clinical decision	Bilirubin < 50 µmol/L and normal albumin and normal renal function: 100% dose Bilirubin ≥ 50 µmol/L or decreased albumin levels: consider 50% dose, increase if tolerated
Cytarabine	GFR ≥ 60 mL/min: 100% dose GFR 31-59 mL/min: 50% dose GFR < 30 mL/min: omit	Mild and moderate: no need for dose adjustment is expected, clinical decision Severe: consider 25-50% of the original dose and increase if tolerated
Cisplatin	GFR ≥ 60 mL/min: 100% dose GFR 50-59 mL/min: 75% dose GFR 40-49 mL/min: 50% dose GFR < 40 mL/min: omit, consider carboplatin	No need for dose adjustment is expected, clinical decision

DRUG INTERACTIONS

Nephrotoxic medications (e.g. NSAIDs, amphotericin, aminoglycosides)	Avoid concomitant use with cisplatin due to additive nephrotoxicity or monitor renal function closely.
Ototoxic medications (e.g. loop diuretics, aminoglycosides)	Avoid concomitant use with cisplatin due to additive ototoxicity, or use with caution and perform regular hearing assessments.
CYP3A4 inhibitors and inducers	Consider potential for increased toxicity (with CYP3A4 inhibitors) and decreased efficacy (with CYP3A4 inducers) of etoposide and methylprednisolone.
Antidiabetic medications	Methylprednisolone may increase blood glucose levels. Patients with diabetes mellitus receiving concurrent insulin and/or oral hypoglycemic agents may require dosage adjustments.
Anti-hypertensives	Hypotension may occur during rituximab administration; therefore, consideration should be given to withholding anti-hypertensives 12 hours prior to the rituximab infusion.

EXTRAVASTATION RISK

Cisplatin: exfoliant
Cytarabine: neutral
Etoposide: irritant
Rituximab: neutral

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

R-ESHAP	Myelosuppression, emesis, alopecia, mucositis
Cisplatin	Nephrotoxicity – ensure the patient receives adequate pre and post hydration. Ototoxicity – assess the patient for tinnitus or hearing abnormalities. Neurotoxicity, diarrhoea, nausea/vomiting.
Cytarabine	CNS toxicity, reversible undesirable effects to the skin, such as erythema, bullous dermatitis, urticaria, vasculitis, alopecia. **"Cytarabine syndrome"** (immuno-allergic effect), characterised by fever, myalgia, bone pain, occasionally chest pain, exanthema, maculopapular rash, conjunctivitis, nausea and malaise (usually occurs 6-12 hours after administration).
Etoposide	Hypotension on rapid infusion, hyperbilirubinaemia
Methyl-prednisolone	Steroid-related side effects may include osteoporosis, hyperglycaemia, hypertension, eye disorders, hypokalaemia, susceptibility to infection, gastrointestinal side-effects (peptic ulceration, indigestion), thinning of the skin. Monitor BMs, BP, electrolytes. Use with caution in patients with co-morbidities, for example, diabetes, cardiovascular diseases, glaucoma.
Rituximab	Chillness, fever, headache, tiredness, aching muscles and joints, itching, redness of skin, nausea and mild drop in blood pressure. **Hepatitis B reactivation** – see pathway for treatment and management of HBV positive patient [LPW.21].

TREATMENT RELATED MORTALITY

1-2%.

REFERENCES

1. Velasquez WS, McLaughlin P, Tucker S, Hagemeister FB, Swan F, Rodriguez MA, Romaguera J, Rubenstein E, Cabanillas F. ESHAP--an effective chemotherapy regimen in refractory and relapsing lymphoma: a 4-year follow-up study. J Clin Oncol. 1994 Jun;12(6):1169-76.
2. Harting R, Venugopal P, Gregory SA, O'Brien T, Bogdanova E. Efficacy and safety of rituximab combined with ESHAP chemotherapy for the treatment of relapsed/refractory aggressive B-cell non-Hodgkin lymphoma. Clin Lymphoma Myeloma. 2007 May;7(6):406-12.
3. Kim MK, Kim S, Lee SS, Sym SJ, Lee DH, Kim SW, Jang S, Park CJ, Chi HS, Huh J, Suh C. Rituximab-ESHAP as a mobilization regimen for relapsed or refractory B-cell lymphomas: a comparison with ESHAP. Transfusion. 2007 Aug; 47(8):1447-54
4. Celltrion Healthcare UK Limited. Truxima® 500 mg concentrate for solution for infusion. Summary of Product Characteristics (SmPC). Last updated 13/12/2022. Available at https://www.medicines.org.uk/emc/ <Last accessed 25/09/2024>
5. medac GmbH. Etoposide 20 mg/ml concentrate for solution for infusion. Last updated 09/02/2024. Available at https://www.medicines.org.uk/emc/ <Last accessed 25/09/2024>
6. Pfizer Limited. Solu-Medrone 500 mg or methylprednisolone sodium succinate for injection. Summary of Product Characteristics (SmPC). Last updated 11/07/2024. Available at https://www.medicines.org.uk/emc/ <Last accessed 25/09/2024>
7. Hospira UK Ltd. Cytarabine 20 mg/ml Solution for Injection/Infusion. Summary of Product Characteristics (SmPC). Last updated 04/04/2024. Available at https://www.medicines.org.uk/emc/ <Last accessed 25/09/2024>
8. Hospira UK Ltd. Cisplatin 1 mg/ml Sterile Concentrate. Summary of Product Characteristics (SmPC). Last updated 10/04/2024. Available at https://www.medicines.org.uk/emc/ <Last accessed 25/09/2024>
9. TVCA Cisplatin hydration guideline. Available at https://thamesvalleycanceralliance.nhs.uk/healthcare-professionals/chemotherapy/ <Last accessed 13/09/2024>
10. Giraud EL, de Lijster B, Krens SD, Desar IME, Boerrigter E, van Erp NP. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Lancet Oncol 2023; 24: e229

CORRESPONDING DOCUMENTS

ESHAP Nursing Care Plan [L.33]

REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung, Haematology Pharmacist	Annual protocol review	May 2017	2.1	
NSSG Lymphoma Group, Cheuk-kie Jackie Cheung, Haematology Pharmacist	Annual protocol review. Ambulatory care information added.	May 2019	2.2	May 2021
Graham Collins, Consultant Haematologist, Natalia Czub, Haematology Pharmacist, NSSG Lymphoma Group	Drug regimen, interactions, dose modifications, contra-indications, references updated. Annual protocol review.	July 2022	3.0	July 2024
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist; NSSG Lymphoma & CLL Group	Pre-assessment [glycaemic control added], concurrent medications [anti-emetics added; gastric protection duration updated]. ESHAP Nursing Care Plan as corresponding document. General formatting. Annual protocol review.	September 2024	3.1	September 2026