R-CVP

[Rituximab, Cyclophosphamide, Vincristine, Prednisolone]

INDICATION

Licensed / NHSE funded: **LYMPHOMA** [ICD-10 codes: C81-86]

- Treatment of adult patients with non-Hodgkin lymphoma (NHL) where more intensive treatment may not be suitable.
- Treatment of advanced stage nodular lymphocyte predominant B-cell lymphoma, also known as nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), rare type of non-classical Hodgkin lymphoma.

Omit rituximab if CD20-negative

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage and IPI of disease - CT scan (neck, chest, abdomen and pelvis), and/or PET-CT scan, presence or absence of B symptoms, clinical extent of disease. Consider bone marrow aspirate and trephine if clinically indicated.
3. Blood tests – FBC, U&Es, LDH, ESR, 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 (refer to [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 NLPHL.** 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.
6. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or had a hysterectomy.
7. ECG +/- ECHO and baseline BP in all patients with a cardiac history or at risk of cardiac complications (hypertension, smokers, diabetes).
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 on the day of treatment.
11. Fertility – it is very important the patient understands the potential risk of infertility, 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. Patients should be adequately hydrated before and after each cycle administration. 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. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Day(s)	Drug	Dose	Route	Administration details
1	Paracetamol Chlorphenamine	1000 mg 10 mg	PO IV	≥ 30 minutes before rituximab
1–5	**PREDNISOLONE**	**40 mg/m² OD**	PO	Take in the morning with food [Day 1 ≥ 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 well tolerated, consider rapid infusion rituximab rate from cycle(s) 2 onwards.
1	**VINCRISTINE***	**1.4 mg/m² [max. 2 mg]**	IV	In 50 mL sodium chloride 0.9% over 10 minutes
1	**CYCLOPHOSPHAMIDE**	**750 mg/m²**	IV	Bolus injection
CYCLE FREQUENCY: 21 days				
TREATMENT DURATION: 6–8 cycles				

*** Vincristine** in patients over 70-year-old – consider capping the dose at 1 mg.

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
Gastric protection	Omeprazole 20mg OD on days 1–5
Anti-emetics Day 1: Moderate risk	▪ Ondansetron on day 1: 8mg BD ▪ Metoclopramide on days 1-4: 10-20mg TDS. For breakthrough nausea or vomiting: 10-20mg TDS when required. For alternative options, refer to [TVCA Anti-emetic guideline].
G-CSF prophylaxis*	Consider if patient is over 70 years of age or is immunosuppressed prior to chemotherapy: Filgrastim **0.5 MU/kg/day**, starting **from day 6** for 5 days
Vitamin D supplement*	If required: Vitamin D < 50 nmol/L: replace as per local formulary
Bone protection*	Refer to the Bone Protection in Lymphoma supportive care guidance [L.132]
Hemorrhagic cystitis prophylaxis* (when required, for example, for patients with pre-existing bladder disorders)	Regimen 1: Mesna PO 300mg/m² (40% of IV cyclophosphamide dose), starting 2 hours before cyclophosphamide injection, 4-hourly for 3 doses. Regimen 2: Mesna IV 150mg/m² (20% of IV cyclophosphamide dose), immediately before cyclophosphamide injection, followed by mesna PO 300mg/m² (40% of IV cyclophosphamide dose) at 2 and 6 hours after the IV mesna dose. In patients at high risk of urothelial toxicity, a shorter interval may be left between mesna doses, the number of doses increased, or both.
PJP prophylaxis*	Consider in relapsed disease. 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.

(*) indicates optional concurrent medications

CONTRAINDICATIONS

Hypersensitivity to active ingredients and excipients. Active severe infections. Discuss with the Consultant in case patient has existing peripheral neuropathy grade 2 or higher. Refer for full details to individual medications Summary of Product Characteristics (SmPCs).

INVESTIGATIONS

Before each cycle: FBC, U&Es, creatinine, LFTs, glucose, bone profile.
When clinically indicated: neurological examination, ECG.

RESTAGING

- Give 3-4 cycles and restage with CT (not needed if clinically assessable disease).
- If progressive disease, consider other treatment.
- If partial remission or complete remission, continue to 6–8 cycles.

DOSE MODIFICATIONS

Discuss treatment modifications with the Consultant.

Hematological toxicities – on the day of treatment – determined by the more severe event.		
Neutrophils [x 10^9/L]*	≥ 1.5	Procced with 100% doses
	1.0 – < 1.5	Give 75% dose of cyclophosphamide, 100% vincristine
	0.5 – < 1.0	Give 50% dose of cyclophosphamide, 100% vincristine
	< 0.5	Omit cyclophosphamide, give 100% vincristine
Platelets [x 10^9/L]	≥ 100	Proceed with 100% doses
	50 – < 100	Give 50% dose of cyclophosphamide, 100% vincristine
	< 50	Omit cyclophosphamide, give 100% vincristine

* Consider G-CSF secondary prophylaxis (after 1 episode of febrile neutropenia)

- **Vincristine:** in the presence of motor weakness or severe sensory symptoms, discuss reducing or withholding vincristine with the Consultant.
- **Prednisolone** dose can be reduced at the Clinician discretion.
- **Rituximab**: dose modifications are not recommended.

Renal impairment	
Vincristine	No need for dose adjustment is expected
Cyclophosphamide	GFR ≥ 30 mL/min: 100% dose GFR 10-29 mL/min: 75% dose GFR < 10 mL/min: omit or consider 50% dose at the Consultant discretion

Hepatic impairment	
Vincristine	Total bilirubin > 51 µmol/l: 50% dose
Cyclophosphamide	Mild and moderate: no need for dose adjustment is expected Severe: not recommended due to risk of reduced efficacy

DRUG INTERACTIONS

CYP3A4 and P-gp inhibitors	Increased risk of vincristine and cyclophosphamide toxicities; when used concurrently, use with caution and monitor closely.
CYP3A4 inducers	Vincristine and cyclophosphamide efficacy can be decreased; when used concurrently, use with caution and monitor closely.
Anti-diabetic medications	Steroids may increase blood glucose levels – monitor closely. Patients with diabetes mellitus receiving concurrent insulin and/or oral hypoglycaemic agents may require dosage adjustments.
Anti-hypertensive medications	Since hypotension may occur during rituximab administration, consider withholding anti-hypertensive medication(s) 12 hours prior to the rituximab infusion.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- Neutropenia and febrile neutropenia - primary prophylaxis with G-CSF is not routinely recommended.
- Alopecia
- Nausea and vomiting – prophylaxis with anti-emetics is recommended.
- Cyclophosphamide may irritate bladder mucosa. Patients should be encouraged to drink minimum of three litres of fluid per 24 hours.
- Vincristine may cause neurotoxicity. It is for intravenous use only; fatal if given by other routes.
- Rituximab may cause patient chillness, fever, headache, tiredness, aching muscles and joints, itching redness of skin, nausea and mild drop in blood pressure.
- Hepatitis B reactivation – following rituximab administration – see pathway for treatment and management of HBV positive patient [LPW.21].
- 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, e.g., diabetes, cardiovascular diseases, glaucoma.

EXTRAVASATION RISK

Rituximab: neutral
Cyclophosphamide: neutral
Vincristine: vesicant

TREATMENT RELATED MORTALITY

1-2%

REFERENCES

1. Marcus R, Imrie K, Solal-Celigny P, Catalano JV, Dmoszynska A, Raposo JC, Offner FC, Gomez-Codina J, Belch A, Cunningham D, Wassner-Fritsch E, Stein G. Phase III Study of R-CVP Compared With Cyclophosphamide, Vincristine, and Prednisone Alone in Patients With Previously Untreated Advanced Follicular Lymphoma. J Clin Oncol. 2008 Jul 28
2. McKay P, Fielding P, Gallop-Evans E, Hall GW, Lambert J, Leach M, Marafioti T, McNamara C. Guidelines for the investigation and management of nodular lymphocyte predominant Hodgkin lymphoma. British journal of haematology. 2016 Jan 1;172(1).
3. NICE. TA243 Rituximab for the first-line treatment of stage III-IV follicular lymphoma. Published Jan 2012. Available at https://www.nice.org.uk/guidance/ta243.
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 02/08/2024>

5. Baxter Healthcare Ltd. Cyclophosphamide Injection 1g. Summary of Product Characteristics (SmPC). Last updated 29/06/2016. Available at https://www.medicines.org.uk/emc/ <Last accessed 02/08/2024>
6. Hospira UK Ltd. Vincristine Sulfate 1 mg/ml Injection. Summary of Product Characteristics (SmPC). Last updated 04/04//2024. Available at https://www.medicines.org.uk/emc/ <Last accessed 02/08/2024>
7. Wockhardt UK Ltd. Prednisolone 5mg tablets. Summary of Product Characteristics (SmPC). Last updated: 25/05/2021. Available online at https://www.medicines.org.uk/emc/ <Last accessed 02/08/2024>
8. Baxter Healthcare Ltd. Mesna Injection. Summary of Product Characteristics (SmPC). Last updated 01/04/2015. Available at https://www.medicines.org.uk/emc/ <Last accessed 02/08/2024>
9. 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

R-CVP Nursing Care Plan [N-L.82]

REVIEW

Name	Revision	Date	Version	Review date
NSSG Lymphoma Group	Annual protocol review	May 2017	3.10	May 2019
NSSG Lymphoma Group	Annual protocol review	May 2019	3.11	May 2021
Quality manager	Nursing care plan added	Oct 2020	3.12	May 2021
Sara Castro, Advanced Haematology Pharmacist	Annual protocol review	April 2021	3.13	May 2023
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist; NSSG Lymphoma & CLL Group	Indications [NLPHL added]. Pre-assessment [glycaemic control advice and irradiated bloods requirement if used for NLPHL added]. Concurrent medications [anti-emetics included, G-CSF duration updated]. Dose modifications updated. R-CVP Nursing Care Plan as corresponding document. General formatting. Annual protocol review.	September 2024	4.0	September 2026