Pola-BR

[Polatuzumab vedotin, Bendamustine, Rituximab]

INDICATIONS

Licensed / NHS funded: **DIFFUSE LARGE B-CELL LYMPHOMA (DLBCL)** [ICD-10 code: C83]

- Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adult patients who are not candidates for haematopoietic stem cell transplantation [NICE TA649 / **Blueteq** required]

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 - 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.
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 [H.8], group and save.
4. Send a "**group and save"** sample to transfusion and ensure patient has been flagged to blood bank for the requirement of **irradiated blood products** for all future transfusions. Refer to [Guidelines for the use of blood components in adult haematology]. Ensure irradiation card is given to the patient.
5. Urine pregnancy test - before cycle 1 of each new chemotherapy course in women of child-bearing age unless they are post-menopausal, have been sterilised or had a hysterectomy.
6. ECG +/- ECHO – if clinically indicated.
7. Record performance status [ECOG].
8. Record vital signs, height and weight.
9. Consent and counseling – 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. Assess and document tumour lysis risk as part of pre-assessment. Patients should be adequately hydrated before and after each cycle administration - in 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]. **When Allopurinol is indicated – advise patients NOT to take it on days of Bendamustine** due to the risk of skin reactions (see DRUG INTERACTIONS below).
12. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

CYCLE 1				
Day(s)	**Drug**	**Dose**	**Route**	**Administration details**
1	Paracetamol Hydrocortisone Chlorphenamine	1000 mg 100 mg 10 mg	PO IV IV	≥ 30 minutes before Rituximab
1	**RITUXIMAB**	**375 mg/m²**	**IV**	In 500 mL sodium chloride 0.9% Refer to [Nursing Care Plans: Rituximab infusion rates], max. rate 400 mg/hour. Patients should be observed for 30 minutes before the start of other infusions. If first dose is well tolerated, consider a rapid infusion rate from cycle 2 onwards.
2	Paracetamol Chlorphenamine	1000 mg 10 mg	PO IV	≥ 30 minutes before Polatuzumab vedotin
2	**POLATUZUMAB VEDOTIN**	**1.8 mg/kg** (max. 240 mg)	**IV**	In 100 mL glucose 5% **over 90 minutes** (using **0.2-µm or 0.22-µm in-line filter**). Patients should be monitored for infusion related reactions (IRRs) during the infusion and for at least **90 minutes** following completion of infusion.
2–3	**BENDAMUSTINE**	**90 mg/m²**	**IV**	In 500 mL sodium chloride 0.9% over 30–60 minutes
CYCLE FREQUENCY: 21 days				

CYCLES 2–6				
Day(s)	**Drug**	**Dose**	**Route**	**Administration details**
1	Paracetamol Hydrocortisone Chlorphenamine	1000 mg 100 mg 10 mg	PO IV IV	≥ 30 minutes before Rituximab
1	**RITUXIMAB**	**375 mg/m²**	**IV**	In 500 mL sodium chloride 0.9% Refer to [Nursing Care Plans: Rituximab infusion rates], max. rate 400 mg/hour. Patients should be observed for 30 minutes before the start of other infusions. If first dose is well tolerated, consider a rapid infusion rate from cycle 2 onwards.
1	**POLATUZUMAB VEDOTIN**	**1.8 mg/kg** (max. 240 mg)	**IV**	In 100 mL glucose 5% **over 30 minutes** (using **0.2-µm or 0.22-µm in-line filter) if previous dose was well tolerated – otherwise, see below*.** Patients should be monitored for infusion-related reactions (IRRs) during the infusion and for at least **30 minutes** following completion of infusion.
1–2	**BENDAMUSTINE**	**90 mg/m²**	**IV**	In 500 mL sodium chloride 0.9% over 30–60 minutes
CYCLE FREQUENCY: 21 days				
TREATMENT DURATION: max. 6 cycles				

***Note:** If the patient experienced an infusion-related reaction **(IRR) to a previous dose of Polatuzumab vedotin**, administer **pre-medications prior to the infusion** (Paracetamol and Chlorphenamine), **infuse over 90 minutes**, and **observe the patient for 90 minutes post-infusion**.

CONCURRENT MEDICATIONS

<table>
<tr><td>TLS prophylaxis
[Cycle 1]</td><td>Refer to the Tumour Lysis Syndrome in Adults protocol [H.8].
Note: Allopurinol should be omitted on the days of Bendamustine.
(See DRUG INTERACTIONS below).
<table><tr><th>TLS risk</th><th>TLS prophylaxis – Cycle 1</th></tr><tr><td>Low</td><td>Hydration + Allopurinol 300mg OD*, starting from day 4 for 7 days</td></tr><tr><td>Intermediate</td><td>Hydration + Allopurinol 300mg OD*, starting 3 days before Bendamustine, then omit on Bendamustine days, and restart from day 4 for 7 days (10 days in total)</td></tr><tr><td>High risk</td><td>Hydration + Rasburicase 3mg on days of chemotherapy, unless otherwise indicated by the Clinician.</td></tr></table>*Reduce dose in renal impairment.</td></tr>
<tr><td>Antiviral prophylaxis</td><td>Aciclovir 200mg TDS during treatment and for 3 months after completion</td></tr>
<tr><td>PJP prophylaxis</td><td>Co-trimoxazole 480mg three times a week on Mon/Wed/Fri for duration of treatment and at least 3 months after completion. Consider reducing the dose to 480 mg twice weekly during neutropenic periods. Pentamidine can be considered for patients who are intolerant or allergic to Co-trimoxazole.</td></tr>
<tr><td>Anti-emetics
Cycle 1 D1: Minimal risk, D2-3: Moderate risk
Cycles 2–6 D1–2: Moderate risk</td><td>▪ Ondansetron 8mg BD (Cycle 1: on days 2–3, Cycles 2–6: on days 1–2)
▪ Metoclopramide 10-20mg TDS (Cycle 1: on days 2–6, Cycles 2–6: on days 1–5). For breakthrough nausea or vomiting: 10-20mg TDS when required.
For alternative options, refer to [TVCA Anti-emetic guideline].</td></tr>
</table>

RESTAGING

After 6 cycles, PET-CT is recommended.
Consider interim CT or PET-CT if there are concerns that the patient is not clinically responding.

INVESTIGATIONS

FBC, U&E, LFTs

TREATMENT MODIFICATIONS

All modifications should be discussed with the Consultant.

Haematological toxicities

<table>
<tr><th colspan="2">On day 1 of each cycle</th></tr>
<tr><td>Delay cycle</td><td>Absolute neutrophil count (ANC) < 1 x 10^9/L or Platelet count < 75 x 10^9/L</td></tr>
<tr><td rowspan="2">Resume treatment when ANC ≥ 1 x 10^9/L and Platelet count ≥ 75 x 10^9/L</td><td>Recovery within 7 days: Restart treatment at the same dose as previous cycle. Add G-CSF support (if not already started).</td></tr>
<tr><td>Recovery more than 7 days: Restart treatment with a dose reduction of Bendamustine (see below). Add G-CSF support (if not already started).
<table><tr><th>Previous Dose of Bendamustine</th><th>Dose reduction to</th></tr><tr><td>90 mg/m^2</td><td>70 mg/m^2</td></tr><tr><td>70 mg/m^2</td><td>50 mg/m^2</td></tr><tr><td>50 mg/m^2</td><td>Discontinue</td></tr></table></td></tr>
</table>

Non-haematological toxicities

Peripheral Neuropathy – Polatuzumab vedotin	
Grade 2–3	▪ Withhold Polatuzumab vedotin. ▪ If symptoms improve to ≤ Grade 1 within 14 days, restart Polatuzumab vedotin at 1.4 mg/kg. ▪ If symptoms do not improve to ≤ Grade 1 OR require > 14 days to recover, discontinue Polatuzumab vedotin permanently.
Grade 4	Discontinue Polatuzumab vedotin permanently.

Infusion Related Reactions (IRRs) – Polatuzumab vedotin	
Grade 1–3	▪ Interrupt the infusion and give supportive treatment. ▪ **The first occurrence** of Grade 3 wheezing, bronchospasm, or generalised urticaria, permanently discontinue Polatuzumab vedotin. ▪ **Recurrent occurrence** of Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue Polatuzumab vedotin. ▪ **Otherwise**, upon complete resolution of symptoms, infusion may be resumed at 50% of the rate achieved prior to interruption. In the absence of infusion-related symptoms, the rate of infusion may be escalated in increments of 50 mg/hour every 30 minutes. ▪ **For the next cycle,** infuse Polatuzumab vedotin over 90 minutes. If no IRRs occur, subsequent infusions may be administered over 30 minutes. Administer pre-medications for all cycles.
Grade 4	Stop infusion immediately and give supportive treatment. Permanently discontinue Polatuzumab vedotin.

	Renal impairment	Hepatic impairment
Bendamustine	GFR > 10 mL/min: 100% dose GFR > 10 mL/min: limited data, clinical decision	Mild (bilirubin < 20 µmol/L): 100% dose Moderate (bilirubin 20–51 µmol/L): 70% dose Severe (bilirubin > 51 µmol/L): not recommended
Polatuzumab vedotin	GFR ≥ 30 ml/min: 100% dose GFR < 30 ml/min: no need for dose adjustment is expected, clinical decision	Mild: 100% dose Moderate and severe: not recommended

DRUG INTERACTIONS

Polatuzumab vedotin	▪ CYP3A4 and P-gp inhibitors: Increased risk of neutropenia due to increased exposure to MMAE (major metabolite of Polatuzumab vedotin). When used concurrently, use with caution and monitor closely. ▪ CYP3A4 inducers: Efficacy of Polatuzumab vedotin may be reduced due to reduced plasma concentrations of MMAE metabolites. When used concurrently, use with caution and monitor closely.
Bendamustine	▪ Concomitant use with CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, aciclovir, cimetidine) may increase Bendamustine concentration. Use with caution. ▪ Cases of Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis have been reported when Bendamustine and Allopurinol were administered concomitantly – avoid concurrent use.
Rituximab	Since hypotension may occur during Rituximab administration, consider withholding anti-hypertensive medication(s) 12 hours prior to infusion.

CONTRAINDICATIONS

Hypersensitivity to active ingredients and excipients. Active severe infections. Severe liver impairment (Bendamustine). Refer for full details to the relevant Summary of Product Characteristics (SmPCs).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Adverse events (AEs) reported in GO29365 trial[1]

- Most common (grade 3/4): anemia, neutropenia, thrombocytopenia, lymphopenia, febrile neutropenia
- Other common (all grades): peripheral neuropathy (majority of G1-2 and reversible), diarrhoea, nausea, fatigue, constipation, pyrexia

Polatuzumab vedotin

- Myelosuppression, peripheral neuropathy, pneumonitis, hepatic impairment, tumour lysis syndrome, serum electrolyte disturbance, infusion-related reactions, joint pain, headache, indigestion.

Rituximab

- Infusion related reactions (IRRs) or severe cytokine release syndrome, characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. **Hepatitis B reactivation** – see the pathway for the management of an HBV-positive patient [LPW.21].

Bendamustine

- Haematological adverse reactions, including leukopenia, thrombocytopenia (dose titration may be required)
- Constitutional symptoms (fever), gastrointestinal symptoms (nausea, vomiting)
- **Infections**: including bacterial (sepsis, pneumonia) and opportunistic infections (Pneumocystis jirovecii pneumonia (PJP), varicella zoster virus (VZV) and cytomegalovirus (CMV)). Cases of progressive multifocal leukoencephalopathy (PML) including fatal ones have been reported following use of Bendamustine mainly in combination with Rituximab or Obinutuzumab. **Hepatitis B reactivation** – see the pathway for the management of an HBV-positive patient. [LPW.21]. Increased mortality (mainly due to opportunistic infections) was observed in recent clinical studies when Bendamustine was used in combination treatment outside the approved indications.
- **Dermatologic toxicities** – allergic reactions, urticaria (common). Cases of Stevens-Johnson syndrome and Toxic Epidermal Necrolysis (TEN) have been reported in patients who received Bendamustine and Allopurinol simultaneously (avoid concurrent use). Patients who experience any skin reactions during treatment, should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious muco-cutaneous reaction, treatment with Bendamustine should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly. Cases of non-melanoma skin cancers (basal cell carcinoma and squamous cell carcinoma) have been reported.
- Refer to the **MHRA advice** for healthcare professionals:
  - [MHRA Drug Safety Update. 2017]. Advise patients to **report promptly any new signs of infection**, including fever or respiratory symptoms, and consider discontinuing Bendamustine if there are signs of opportunistic infections. Monitor patients for opportunistic infections as well as cardiac, neurological, and respiratory adverse events. Monitor known carriers of **HBV** for signs and symptoms of active HBV infection. Report suspected adverse reactions associated with Bendamustine to MHRA via [Yellow Card], including those associated with off-label use.
  - [MHRA Drug Safety Update. 2021]. Periodically perform **skin examinations** in patients on Bendamustine-containing regimens and **consider PML** in the differential diagnosis for patients on Bendamustine with new or worsening neurological, cognitive, or behavioural signs or symptoms.

EXTRAVASATION RISK

Bendamustine: vesicant / irritant
Polatuzumab vedotin: neutral
Rituximab: neutral

TREATMENT RELATED MORTALITY

Estimated 5–10%

REFERENCES

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2. NICE. Polatuzumab vedotin with rituximab and bendamustine for treating relapsed or refractory diffuse large B-cell lymphoma [TA649]. Published and last updated 23/09/2020. Available at https://www.nice.org.uk/guidance/ta649 <Last accessed 25/09/2024>
3. Roche Products Limited. Polivy ® (Polatuzumab vedotin) 140 mg powder for concentrate for solution. Summary of Product Characteristics (SmPCs). Last updated 20/07/2022. Available online at https://www.medicines.org.uk/emc/ <Last accessed 25/09/2024>
4. Celltrion Healthcare UK Limited. Truxima® 500 mg concentrate for solution for infusion. Summary of Product Characteristics (SmPC). Last updated 09/06/2025. Available at https://www.medicines.org.uk/emc/ <Last accessed 25/09/2025>
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6. MHRA. Drug Safety Update. Bendamustine (Levact): increased mortality observed in recent clinical studies in off-label use; monitor for opportunistic infections, hepatitis B reactivation. Published 20/07/2017. Available at https://www.gov.uk/drug-safety-update/bendamustine-levact-increased-mortality-observed-in-recent-clinical-studies-in-off-label-use-monitor-for-opportunistic-infections-hepatitis-b-reactivation <Last accessed 25/09/2024>
7. MHRA. Drug Safety Update. Bendamustine (Levact): increased risk of non-melanoma skin cancer and progressive multifocal encephalopathy (PML). Published 24/03/2021. Available at https://www.gov.uk/drug-safety-update/bendamustine-levact-increased-risk-of-non-melanoma-skin-cancer-and-progressive-multifocal-encephalopathy-pml#contents <Last accessed 25/09/2024>
8. 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

REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung, Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist	New document	Jul 2019	1.0	May 2020
Nadjoua Maouche, Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist	Update following NICE approval, trial publication and Licensing.	September 2020	2.0	May 2023
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, NSSG Lymphoma & CLL Group	Contraindications, Drug interactions added. Adverse reactions, References updated. MHRA advice on Bendamustine use added. General formatting. Annual protocol review.	September 2024	3.0	September 2027