Polatuzumab vedotin + Bendamustine + Rituximab (PBR)

INDICATIONS
Relapsed or refractory diffuse large B-cell lymphoma (DLBCL) in adult patients who are ineligible for stem cell transplant (NICE approved 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 aspirations 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. Send a "group and save" sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions. Ensure irradiation card is attached to the patient's notes and copy given to the patient. See 'Guidelines for the use of blood components in adult haematology'.
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 undergone a hysterectomy.
6. ECG +/- Echo.
7. Record performance status, 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.
9. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice (see fertility guidelines).
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. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
12. Treatment should be agreed in the relevant MDT.
**DRUG REGIMEN**

**Cycle 1**

**Day 1**  
*Pre med* - paracetamol 1g PO, chlorphenamine 10 mg IV, hydrocortisone 100 mg IV 30 minutes before rituximab.

RITUXIMAB 375 mg/m² IV infusion in 500 mL sodium chloride 0.9%  
(Refer to rituximab care plan for titration of infusion rate. If first dose well tolerated, consider rapid infusion rituximab from dose 2 onwards).

**Days 2**  
*Pre med* - paracetamol 1g PO, chlorphenamine 10 mg IV 30 minutes before polatuzumab vedotin.

POLATUZUMAB VEDOTIN 1.8 mg/kg (maximum 240mg) in 100 mL glucose 5% IV infusion over 90 minutes, administer via low-protein binding in line filter with 0.2 or 0.22micrometer pore size Observe patient for IRRs during the infusion and for 90 minutes after completion. ().

**Days 2 to 3**  
BENDAMUSTINE 90 mg/m² IV infusion daily in 500 mL sodium chloride 0.9% over 30-60 minutes.  
NOTE: Interaction with allopurinol – see under ‘Concurrent medications’.

**Cycle 2 to 6**

**Day 1**  
*Pre med* - paracetamol 1g PO, chlorphenamine 10 mg IV, hydrocortisone 100 mg IV 30 minutes before rituximab.

RITUXIMAB 375 mg/m² IV infusion in 500 mL sodium chloride 0.9%  
(Refer to rituximab care plan for titration of infusion rate. If first dose well tolerated, consider rapid infusion rituximab from dose 2 onwards).

POLATUZUMAB VEDOTIN 1.8 mg/kg (maximum 240mg) in 100 mL glucose 5% IV infusion over 30 minutes*, administer via low-protein binding in line filter with 0.2 or 0.22micrometer pore size, Observe patient for IRRs during the infusion and for 30 minutes* after completion.  
(*Note: If patient had previous infusion-related reaction, administer pre-med prior to infusion and give polatuzumab vedotin over 90 minutes and observe for 90 minutes afterwards)

**Days 1 to 2**  
BENDAMUSTINE 90 mg/m² IV infusion daily in 500 mL sodium chloride 0.9% over 30-60 minutes.  
NOTE: Interaction with allopurinol – see under ‘Concurrent medications’.

**CYCLE FREQUENCY**

Cycle repeats every 21 days to a maximum of 6 courses.
RESTAGING

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

DOSE MODIFICATIONS

Haematological Toxicity

<table>
<thead>
<tr>
<th>On day 1 of each cycle</th>
<th>Withhold treatment, and if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil &lt;1 x 10^9/L or Platelet &lt;75 x 10^9/L</td>
<td>Recovery within 7 days (Neutrophil ≥ 1 x 10^9/L and Platelet ≥75 x 10^9/L) Resume treatment at the same dose as previous cycle. Add GCSF support.</td>
</tr>
<tr>
<td></td>
<td>Recovery more than 7 days (Neutrophil ≥ 1 x 10^9/L and Platelet ≥75 x 10^9/L) Restart treatment with a dose reduction on Bendamustine. Add GCSF support.</td>
</tr>
</tbody>
</table>

Polatuzumab vedotin

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose adjustment is required with CrCl ≥30mL/min. No data available for patient with CrCl &lt; 30mL/min.</td>
<td>No dose adjustment required for mild hepatic impairment (bilirubin ≤1.5 x ULN, or AST&gt;ULN). Avoid in moderate to severe hepatic impairment (bilirubin &gt;1.5 x ULN).</td>
</tr>
</tbody>
</table>

Peripheral Neuropathy

Grade 2 - 3: Withhold polatuzumab vedotin.
- If symptom improves to ≤ Grade 1 within 14 days, restart polatuzumab vedotin at 1.4mg/kg.
- If symptom does not improve to ≤ Grade 1 OR requires >14 days to recover, discontinue polatuzumab vedotin permanently.

Grade 4: Discontinue polatuzumab vedotin permanently.

Polatuzumab vedotin Infusion Related Reactions (IRRs)

<table>
<thead>
<tr>
<th>Severity of IRR</th>
<th>Modifications</th>
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</thead>
<tbody>
<tr>
<td>Grade 1-2</td>
<td>First occurrence:</td>
</tr>
</tbody>
</table>

This is a controlled document and therefore must not be changed or photocopied
Interrupt the infusion and give supportive treatment.

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 occurs, subsequent infusions may be administered over 30 minutes. Administer premedication for all cycles.

**Recurrent IRRs:**
- For recurrent Grade 2 wheezing or urticaria, or for recurrence of permanently discontinue polatuzumab vedotin.

### Bendamustine

<table>
<thead>
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<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
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<tbody>
<tr>
<td>CrCl &gt;10 mL/min</td>
<td>100% dose</td>
</tr>
<tr>
<td>Mild Bili &lt;20 micromol/L</td>
<td>100% dose</td>
</tr>
<tr>
<td>Moderate Bili 20-51 micromol/L</td>
<td>70% dose</td>
</tr>
<tr>
<td>Severe Bili &gt;51 micromol/L</td>
<td>No data available *</td>
</tr>
</tbody>
</table>

**CONCURRENT MEDICATION**

- **Allopurinol**
  (see ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS below).
  - There have been rare skin reactions and other toxicities associated with the administration of allopurinol and Bendamustine when given together. It is suggested that allopurinol is omitted on the days of Bendamustine administration.
  - Low tumour lysis risk: allopurinol should be commenced following the administration of Bendamustine (i.e. day 3) at a dose of 300 mg OD.
  - Intermediate tumour lysis risk (low grade with bulk): allopurinol 300mg OD for 3 days prior to the administration of Bendamustine and for 5-7 days following Bendamustine.

- **Aciclovir**
  - 200 mg 3 times daily for duration of chemotherapy and for 3 months after completion.

- **Co-trimoxazole**
  - 480 mg daily on Monday / Wednesday / Friday for duration of treatment and for 3 months afterwards (consider reducing the dose to 480 mg twice weekly during neutropenic periods).

**INVESTIGATIONS**

FBC, U&E, LFT.

**EMETIC RISK**

Moderate (avoid the use of Dexamethasone).
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The most common G3/4 adverse events reported in GO29365 trial include: anemia (28%), neutropenia (46%), thrombocytopenia (41%), infections (23%), febrile neutropenia (10%). Other commonly reported AEs of all grades: peripheral neuropathy (43%, majority of G1-2 and reversible), diarrhea (38%), nausea (30%), fatigue (35%), constipation (17%), pyrexia (33%).

**Polatuzumab vedotin** – myelosuppression, peripheral neuropathy, pneumonitis, hepatic impairment, tumour lysis syndrome, serum electrolyte disturbance, infusion-related reaction, joint pain, headache, indigestion and hepatitis B reactivation – see pathway for treatment and management of HBV positive patient. There is potential interaction with strong CYP3A4 inducer and inhibitor – use with caution.

**Bendamustine** - myelosuppression (dose titration may be required), hypersensitivity, liver enzyme rise, arrhythmia, possible risk of secondary malignancies and increased risk of opportunistic infections. Hepatitis B virus (HBV) reactivation has also been reported. Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients who received Bendamustine and allopurinol simultaneously. If patients experience any skin reactions during treatment, they should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious mucocutaneous 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.

**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, and hepatitis B reactivation.

All patients who are at risk of tumour lysis syndrome (TLS) must receive prophylaxis prior to initiation of treatment. An appropriate hydration regimen (a fluid intake of approximately 3 L per day) starting before treatment is mandatory. Taking into account the degree of TLS risk and existing co-morbidities, the administration of allopurinol or an alternative can be considered if clinically appropriate. All patients should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values.

**EXTRAVASATION RISK**

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

**TREATMENT RELATED MORTALITY**

Estimated 5-10%.

**REFERENCES**
2.  NICE TA
4.  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. [Link]

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Cheuk-kie Jackie Cheung (Haematology Pharmacist), Dr Graham Collins (Consultant Haematologist)</td>
<td>New document</td>
<td>Jul 2019</td>
<td>1.0</td>
<td>May 2020</td>
</tr>
<tr>
<td>Nadjoua Maouche (Haematology Pharmacist) Dr Graham Collins (Consultant Haematologist)</td>
<td>Update following NICE approval, trial publication and Licensing.</td>
<td>September 2020</td>
<td>2.0</td>
<td>May 2023</td>
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