# Polatuzumab vedotin, Rituximab, Doxorubicin, Cyclophosphamide & Prednisolone (POLA-R-CHP)

## Indication

First line treatment of CD20 positive diffuse large B-Cell lymphoma (DLBCL) in adults with an International Prognostic Index (IPI) score of 2 to 5.

NICE TA874

## ICD-10

C83.3, C83.8, C85.2

## Regimen details

**Cycles 1-6**

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1* | Rituximab | 375mg/m$^2$ | IV infusion |
| 1 | Polatuzumab vedotin | 1.8mg/kg | IV infusion |
| 1 | Doxorubicin | 50mg/m$^2$ | IV bolus |
| 1 | Cyclophosphamide | 750mg/m$^2$ | IV bolus/infusion |
| 1-5 | Prednisolone | 100mg | PO |

* For cycle 1, treatment may be split over 2 days with Rituximab given on day 0 and polatuzumab vedotin, doxorubicin and cyclophosphamide given on day 1.

**Cycles 7-8***

| Day | Drug | Dose | Route |
|---|---|---|---|
| 1 | Rituximab | 375mg/m$^2$ | IV infusion |

## Cycle frequency

21 days

## Number of cycles

6-8 cycles (*clinical decision for cycles 7 & 8).

## Administration

Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased at 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100 mg/hour and if tolerated increased at 100mg/hour increments every 30minutes to a maximum of 400 mg/hour.

Polatuzumab vedotin is administered in in 50-100mL glucose 5% or sodium chloride 0.9% (final concentration between 0.72-2.7mg/mL) via a low-protein binding 0.22 micron in-line filter. The first dose should be administered over 90 minutes, followed by a 90 minute observation period. If no reaction observed, subsequent infusions can be given over 30 minutes, with an additional 30 minute post-infusion observation period.

Doxorubicin is administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%.

Cyclophosphamide is administered as an IV bolus or as an IV infusion in 250-500mL sodium chloride 0.9% over 30

minutes.

Prednisolone is available as 5mg and 25mg tablets. The dose should be taken each morning for 5 days with or after food. On days of monoclonal antibody give ≥ 30 minutes pre-treatment.

Polatuzumab vedotin, rituximab, cyclophosphamide and doxorubicin may be administered in any order as along as the prednisolone is administered first.

## Pre-medication

Consider steroid prephase (prednisolone 50-100mg OD for 5-7 days).
Consider IV hydration for patients with bulky disease.
Antiemetics as per local policy.
**Rituximab premedication:**

- Paracetamol 1g PO 60 minutes prior to rituximab infusion.
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion.
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion (may be omitted if day 1 prednisolone has been taken at least 30 minutes prior to the start of the rituximab infusion).

**Polatuzumab premedication, if not already pre-medicated for rituximab:**

- Paracetamol 1g PO 60 minutes prior to polatuzumab vedotin infusion.
- Chlorphenamine 10mg IV bolus 15 minutes prior to polatuzumab vedotin infusion.

## Emetogenicity

This regimen has moderate – high emetic potential.

## Additional supportive medication

Tumour lysis syndrome (TLS) prophylaxis – risk stratification and management as per local policy.
Proton-pump inhibitor or H2 antagonist as per local policy.
Antiemetics as per local policy.
Antiviral and antifungal prophylaxis as per local policy.
Pneumocystis jirovecii pneumonia prophylaxis as per local policy.
G-CSF is given as primary prophylaxis in cycles 1-6 (starting on day 6 for 5-7 days)
Loperamide as required.
Bone protection as per local policy
Consider Mesna if known bladder disorder predisposing to haemorrhagic cystitis.

## Extravasation

Rituximab and cyclophosphamide are neutral (group 1)
Polatuzumab vedotin is irritant (group 3)
Doxorubicin is vesicant (group 5)

## Investigations – pre first cycle

| Investigation | Validity period |
|---|---|
| FBC | 14 days |
| U+E, Creatinine | 14 days |
| Liver Function Tests | 14 days |

Other pre-treatment investigations & assessments:
Calcium, LDH, TLS risk, glucose
HIV, Hepatitis B, and C serology
If clinical suspicion of cardiac dysfunction: ECHO and/or MUGA
Assess for neuropathy

## Investigations – pre subsequent cycles

| Investigation | Validity period |
|---|---|
| FBC | 96 hours |
| U+E (including creatinine) | 7 days |
| LFTs | 7 days |

Other pre-treatment investigations & assessments:
Neuropathy assessment

## Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

| Investigation | Limit |
|---|---|
| Neutrophils | ≥ 1.0 x $10^9$/L |
| Platelets | ≥ 75 x $10^9$/L |
| Creatinine clearance (CrCl) | > 30 mL/min |
| Bilirubin | ≤ ULN |
| ALT | ≤ 2 x ULN |

## Dose modifications

- **Haematological toxicity**

| On day 1 of each cycle | | |
|---|---|---|
| Neutrophils <1.0x$10^9$/L or Platelets <75 x $10^9$/L | Withhold treatment, and if: | |
| | Recovery within 7 days | Resume treatment at the same dose as previous cycle |
| | Recovery more than 7 days<br>or<br>Febrile neutropenia | When restarting treatment, consider a dose reduction of cyclophosphamide and/or doxorubicin by 25-50%. If cyclophosphamide and/or doxorubicin are already reduced by 25%, consider reducing one or both agents to 50%. |

- **Renal impairment**

Rituximab – no need for dose adjustment

Polatuzumab vedotin – no data available in patients with severe renal impairment (CrCl <30ml/min)

Doxorubicin and Cyclophosphamide

| CrCl (ml/min) | Doxorubicin dose | Cyclophosphamide dose |
|---|---|---|
| >20 | 100% | 100% |
| 10-20 | 100% | 75% |
| <10 | Discuss with consultant. | Consider reducing dose to 50% |

- **Hepatic impairment**

Rituximab – no need for dose adjustment.

Polatuzumab vedotin

| **Bilirubin** (µmol/L) | **Polatuzumab vedotin dose** |
|---|---|
| ≤ 1.5 x ULN | 100% |
| > 1.5 x ULN | Not recommended |

Doxorubicin

| **Bilirubin** (x ULN) | | **AST/ALT** (x ULN) | **Doxorubicin dose** |
|---|---|---|---|
| <ULN | and | <2 | 100% |
| <ULN | and | 2 - 3 | 75% |
| 1 - 2.5 | or | >3 | 50% |
| 2.5 - 4 | | | 25% |
| > 4 | | | Omit |

Cyclophosphamide

| **Bilirubin** (x ULN) | **Cyclophosphamide dose** |
|---|---|
| <2.5 | 100% |
| 2.5-4.0 | 75% |
| >4.0 | Not recommended. Decreased activation of cyclophosphamide in severe hepatic impairment, discuss with consultant. |

- **Other toxicities**

| **Toxicity** | **Definition** | **Dose adjustment** |
|---|---|---|
| Peripheral neuropathy | Grade 2 | Sensory neuropathy:<br>• Reduce polatuzumab vedotin to 1.4 mg/kg.<br>• If Grade 2 persists or recurs at day 1 of a future cycle, reduce polatuzumab vedotin to 1.0 mg/kg.<br>• If already at 1.0 mg/kg and Grade 2 occurs at day 1 of a future cycle, discontinue polatuzumab vedotin.<br><br>Motor neuropathy:<br>• Withhold polatuzumab vedotin dosing until improvement to Grade ≤1.<br>• Restart polatuzumab vedotin at the next cycle at 1.4 mg/kg.<br>• If already at 1.4 mg/kg and Grade 2 occurs at day 1 of a future cycle, withhold polatuzumab vedotin dosing until improvement to Grade ≤ 1. Restart polatuzumab vedotin at 1.0 mg/kg.<br>• If already at 1.0 mg/kg and Grade 2 occurs at day 1 of a future cycle, discontinue polatuzumab vedotin.<br><br>If concurrent sensory and motor neuropathy, follow the most severe restriction recommendation above. |

| | | |
|---|---|---|
| | Grade 3 | Sensory neuropathy:<br>• Withhold polatuzumab vedotin dosing until improvement to Grade ≤ 2.<br>• Reduce polatuzumab vedotin to 1.4 mg/kg.<br>• If already at 1.4 mg/kg, reduce polatuzumab vedotin to 1.0 mg/kg. If already at 1.0 mg/kg, discontinue polatuzumab vedotin.<br><br>Motor neuropathy:<br>• Withhold polatuzumab vedotin dosing until improvement to Grade ≤ 1.<br>• Restart polatuzumab vedotin at the next cycle at 1.4 mg/kg.<br>• If already at 1.4 mg/kg and Grade 2–3 occurs, withhold polatuzumab vedotin dosing until improvement to Grade ≤ 1. Restart polatuzumab vedotin at 1.0 mg/kg.<br>• If already at 1.0 mg/kg and Grade 2–3 occurs, discontinue polatuzumab vedotin.<br><br>If concurrent sensory and motor neuropathy, follow the most severe restriction recommendation above. |
| | Grade 4 | Discontinue polatuzumab vedotin |
| Infusion related reactions | Grade 1-3 *(except G3 wheezing, bronchospasm or urticaria or recurrent G2/G3 symptoms – see below)* | Interrupt polatuzumab vedotin infusion and give supportive treatment.<br><br>Upon resolution of symptoms, resume polatuzumab vedotin infusion at 50% of the rate achieved prior to interruption. In the absence of further IRR, the rate of the infusion may be escalated in increments of 50mg/hr every 30 minutes.<br>For the next cycle infuse polatuzumab vedotin over 90 minutes, if no further IRR, subsequent infusions may be administered over 30 minutes. Administer pre-medication for all future cycles. |
| | Grade 3 wheezing, bronchospasm or urticaria *Or*<br>Recurrent Grade 2 wheezing or urticaria<br>*Or*<br>Any recurrent Grade 3 symptoms<br>*Or*<br>Grade 4 IRR | Stop polatuzumab vedotin infusion immediately.<br><br>Give supportive treatment.<br><br>Permanently discontinue polatuzumab vedotin |

## **Adverse effects** - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Hypersensitivity reactions
Cytokine release syndrome

Steven-Johnson syndrome, toxic epidermal necrolysis
Tumour lysis syndrome, renal impairment
Increased risk of opportunistic infections
Pneumonitis
Hepatitis B reactivation
Cardiotoxicity, arrhythmias
Peripheral neuropathy
Infertility/early menopause
Secondary malignancy

- **Frequently occurring side effects**

Constipation, diarrhoea
Fatigue
Nausea and vomiting
Infection / neutropenic fever
Alopecia
Mucositis, stomatitis
Hypokalaemia

- **Other side effects**

Fluid retention
Haemorrhagic cystitis
Insomnia
Raised transaminases
Rash, urticaria

## Significant drug interactions – for full details consult product literature/ reference texts

**Warfarin/coumarin anticoagulants:** increased or fluctuating anticoagulant effects. Consider alternative agents or closer monitoring.

**Polatuzumab vedotin**
**Strong CYP3A4 and P-gp inhibitors** (e.g. ketoconazole) may increase the area under the concentration-time curve (AUC) of unconjugated MMAE (the cytotoxic component of polatuzumab vedotin) by 48%.
**Strong CYP3A4 inhibitors** (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) – potential for increased unconjugated MMAE levels, monitor more closely for signs of toxicities.
**Strong CYP3A4 inducers** (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort) may decrease the exposure of unconjugated MMAE.

**Cyclophosphamide**
**Amiodarone:** increased risk of pulmonary fibrosis – avoid if possible
**Clozapine:** increased risk of agranulocytosis – avoid concomitant use
**Digoxin tablets:** reduced absorption – give as liquid form
**Itraconazole:** may increase adverse effects of cyclophosphamide
**Phenytoin:** reduced absorption - may need to increase dose of phenytoin
**Grapefruit juice:** decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

## Additional comments

Where appropriate counsel regarding for contraception with both male and female patients.

Doxorubicin has a lifetime maximum cumulative dose of 450mg/$m^2$.

## References


- Tilly, H., et al. Polatuzumab Vedotin in Previously Untreated Diffuse Large B-Cell Lymphoma. *N Engl J Med 2022; 386:351-363*
- Malpica L et al A retrospective study on prephase therapy prior to definitive multiagent chemotherapy in aggressive lymphomas. *Leuk Lymphoma. 2020 Jun; 61(6): 1508–1511.*
- NICE, 2023. Polatuzumab vedotin in combination for untreated diffuse large B-cell lymphoma [TA874]. Accessed 13/03/2023 via https://www.nice.org.uk/guidance/TA874
- Summary of Product Characteristics: Cyclophosphamide (Sandoz) 1000mg powder for solution for injection or infusion. Accessed 13/03/2023 via https://www.medicines.org.uk
- Summary of Product Characteristics: Doxorubicin (Medac) 2mg/ml solution for infusion. Accessed 13/03/2023 via https://www.medicines.org.uk
- Summary of Product Characteristics: Rituximab (Rixathon) 500mg concentrate for solution for infusion. Accessed 13/03/2023 via https://www.medicines.org.uk
- Summary of Product Characteristics: Polatuzumab vedotin (Polivy) 140mg powder for concentrate for solution for infusion. Accessed 13/03/2023 via https://www.medicines.org.uk


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