

## 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 <sup>2</sup>	IV infusion
1	Polatuzumab vedotin	1.8mg/kg	IV infusion
1	Doxorubicin	50mg/m <sup>2</sup>	IV bolus
1	Cyclophosphamide	750mg/m <sup>2</sup>	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 <sup>2</sup>	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 100mL glucose 5% or sodium chloride 0.9% 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  $\geq 30$  minutes pre-treatment.

Polatuzumab vedotin, rituximab, cyclophosphamide and doxorubicin may be administered in any order as long 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	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 75 \times 10^9/L$
Creatinine clearance (CrCl)	$> 30 \text{ mL/min}$
Bilirubin	$\leq \text{ULN}$
ALT	$\leq 2 \times \text{ULN}$

### Dose modifications

- **Haematological toxicity**

On day 1 of each cycle		
Neutrophils $< 1.0 \times 10^9/L$ or Platelets $< 75 \times 10^9/L$	Withhold treatment, and if:	
	Recovery within 7 days	Resume treatment at the same dose as previous cycle
	Recovery more than 7 days or 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  $< 30 \text{ mL/min}$ )

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 ( $\mu\text{mol/L}$ )	Polatuzumab vedotin dose
$\leq 1.5 \times \text{ULN}$	100%
$> 1.5 \times \text{ULN}$	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	<p>Sensory neuropathy:</p> <ul style="list-style-type: none"> <li>Reduce polatuzumab vedotin to 1.4 mg/kg.</li> <li>If Grade 2 persists or recurs at day 1 of a future cycle, reduce polatuzumab vedotin to 1.0 mg/kg.</li> <li>If already at 1.0 mg/kg and Grade 2 occurs at day 1 of a future cycle, discontinue polatuzumab vedotin.</li> </ul> <p>Motor neuropathy:</p> <ul style="list-style-type: none"> <li>Withhold polatuzumab vedotin dosing until improvement to Grade <math>\leq 1</math>.</li> <li>Restart polatuzumab vedotin at the next cycle at 1.4 mg/kg.</li> <li>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 <math>\leq 1</math>. Restart polatuzumab vedotin at 1.0 mg/kg.</li> <li>If already at 1.0 mg/kg and Grade 2 occurs at day 1 of a future cycle, discontinue polatuzumab vedotin.</li> </ul> <p>If concurrent sensory and motor neuropathy, follow the most severe restriction recommendation above.</p>

	Grade 3	<p>Sensory neuropathy:</p> <ul style="list-style-type: none"> <li>Withhold polatuzumab vedotin dosing until improvement to Grade <math>\leq 2</math>.</li> <li>Reduce polatuzumab vedotin to 1.4 mg/kg.</li> <li>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.</li> </ul> <p>Motor neuropathy:</p> <ul style="list-style-type: none"> <li>Withhold polatuzumab vedotin dosing until improvement to Grade <math>\leq 1</math>.</li> <li>Restart polatuzumab vedotin at the next cycle at 1.4 mg/kg.</li> <li>If already at 1.4 mg/kg and Grade 2–3 occurs, withhold polatuzumab vedotin dosing until improvement to Grade <math>\leq 1</math>. Restart polatuzumab vedotin at 1.0 mg/kg.</li> <li>If already at 1.0 mg/kg and Grade 2–3 occurs, discontinue polatuzumab vedotin.</li> </ul> <p>If concurrent sensory and motor neuropathy, follow the most severe restriction recommendation above.</p>
	Grade 4	Discontinue polatuzumab vedotin
Infusion related reactions	Grade 1-3 ( <i>except G3 wheezing, bronchospasm or urticaria or recurrent G2/G3 symptoms – see below</i> )	<p>Interrupt polatuzumab vedotin infusion and give supportive treatment.</p> <p>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.</p> <p>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.</p>
	Grade 3 wheezing, bronchospasm or urticaria <i>Or</i> Recurrent Grade 2 wheezing or urticaria <i>Or</i> Any recurrent Grade 3 symptoms <i>Or</i> Grade 4 IRR	<p>Stop polatuzumab vedotin infusion immediately.</p> <p>Give supportive treatment.</p> <p>Permanently discontinue polatuzumab vedotin</p>

**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<sup>2</sup>.

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## 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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