Polatuzumab vedotin, Bendamustine & Rituximab (PBR) (Lymphoma)

Indication

Relapsed or refractory Diffuse Large B Cell lymphoma (DLBCL) in adults who are NOT candidates for haematopoietic stem cell transplant

NICE TA649

ICD-10 codes

C83.3, C83.8, C85.2

Regimen details

Day	Drug	Dose	Route
0 or 1	Rituximab	375mg/m^2	IV infusion
1	Polatuzumab Vedotin	1.8mg/kg (max 240mg*)	IV infusion
1 and 2	Bendamustine	90mg/m^2	IV infusion

* due to limited clinical experience in patients treated with 1.8mg/kg Polivy at a total dose >240mg, it is recommended not to exceed the dose of 240mg per cycle.

Cycle frequency

Every 21 days

Number of cycles

6 cycles

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 100 mL glucose 5% 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.

Bendamustine is administered in 500ml sodium chloride 0.9% over 30-60 minutes.

Pre-medication

Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 8mg IV or hydrocortisone 100mg IV bolus 15 minutes prior to 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 emetic potential

Additional supportive medication

Tumour lysis syndrome (TLS) prophylaxis – refer to local guidelines for risk stratification and management. (NB. If allopurinol is used this can increase the risk of skin toxicity when given with bendamustine. Omit allopurinol on days of bendamustine administration.)
Antiviral and antifungal prophylaxis as per local policy
PCP prophylaxis as per local policy
Consider GCSF support as per local policy.

Extravasation

Rituximab is neutral (group 1)
Polatuzumab vedotin is irritant (group 3)
Bendamustine is irritant (group 3)

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

Additional investigations:
If high risk of TLS, check baseline calcium, phosphate, uric acid, LDH, within 14 days of first cycle.
Hepatitis B core antibody and surface antigen, hepatitis C antibody, HIV viral screen.

Investigations – pre subsequent cycles

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

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	≤ 20 µmol/L
ALT	< 2.5 x ULN

Dose modifications

- **Haematological toxicity**

On day 1 of each cycle		
Neutrophil <1.0 x10^9/L or Platelet <75 x10^9/L	Withhold treatment, and if:	
	Recovery within 7 days	Resume treatment at the same dose as previous cycle, consider GCSF support for neutropenia.
	Recovery more than 7 days	Restart with a dose reduction in Bendamustine (from 90mg/m^2 to 70mg/m^2, or if already on 70mg/m^2 to 50mg/m^2), consider GCSF support for neutropenia.

- **Renal impairment**

Bendamustine – if CrCl <10ml/min, not recommended.

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

Rituximab – no need for dose adjustment

- **Hepatic impairment**

Bendamustine

Bilirubin (µmol/L)	**Bendamustine dose**
<20	100%
20-51	70%
>51	Not recommended

Polatuzumab vedotin

Bilirubin (µmol/L)	**Polatuzumab vedotin dose**
<32	100%
≥32	Not recommended

Rituximab – no need for dose adjustment

- **Other toxicities**

Toxicity	**Definition**	**Dose adjustment**
Peripheral neuropathy	Grade 2-3	Withhold polatuzumab vedotin. Restart at 1.4mg/kg if symptom improves to ≤ Grade 1 within 14 days, otherwise discontinue
	Grade 4	Discontinue polatuzumab vedotin
Infusion related reactions	Grade 1-3 *(except G3 wheezing, bronchospasm or urticaria or recurrent G2/G3 symptoms – see below)*	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. For the next cycle infuse over polatuzumab vedotin over 90 minutes, if no further IRR, subsequent infusions may be administered over 30 minutes. Administer pre-medication for all future cycles.

Infusion related reactions (cont'd)	Grade 3 wheezing, bronchospasm or urticaria *Or* Recurrent Grade 2 wheezing or urticaria *Or* Any recurrent Grade 3 symptoms *Or* Grade 4 IRR	Permanently discontinue polatuzumab vedotin

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

- **Serious side effects**

Myelosuppression
Hypersensitivity reactions
Arrhythmias
Secondary malignancies
Increased risk of opportunistic infections
Pneumonitis
Hepatitis B reactivation
Cytokine release syndrome
Stevens-Johnson syndrome, Toxic epidermal necrolysis (Bendaustine with allopurinol)
Tumour lysis syndrome
Infertility

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoes, constipation
Hypokalaemia
Renal impairment

- **Other side effects**

Raised transaminases
Alopecia
Fatigue
Insomnia
Rash, urticaria

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

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Bendamustine

Allopurinol: reports of Stevens-Johnson syndrome and toxic epidermal necrolysis – avoid concurrent administration.

CYP 1A2 inhibitors: metabolism of bendamustine by cytochrome P450 (CYP) 1A2 isoenzyme is a significant route of hepatic clearance so interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine is possible. May increase toxicity – avoid concomitant use.

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 levelsmonitor 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.

Additional comments

Patients must receive irradiated blood products for all future transfusions.

References

- National Institute for Health and Care Excellence. TA649 accessed 7 February 2023 via www.nice.org.uk
- Summary of Product Characteristics Bendamustine (Seacross) accessed 7 February 2023 via www.medicines.org.uk
- Summary of Product Characteristics Polatuzumab vedotin (Roche) accessed 7 February 2023 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) accessed 7 February 2023 via www.medicines.org.uk
- Sehn, LH. *et al*. Polatuzumab Vedotin in Relapsed or Refractory Diffuse Large B-Cell Lymphoma. J Clin Oncol 2020 30(2):155-165

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