PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Polatuzumab Vedotin, Rituximab and Bendamustine Diffuse Large B Cell Lymphoma (DLBCL)

PROTOCOL REF: MPHAPOLVHA
(Version No. 2.0)

Approved for use in:

- Previously treated adult patients with relapsed or refractory diffuse large B-cell lymphoma and who are not candidates for haematopoietic stem cell transplantation.
- Polatuzumab vedotin given in combination with bendamustine and rituximab.
- ECOG performance status 0-2
- Patient has not had previous treatment with bendamustine, or received response duration of >1 year with previous bendamustine treatment.
- Treatment breaks of up to 6 weeks beyond the expected 3-weekly cycle length are allowed but solely to allow toxicities to resolve.

Blueteq registration is required

Dosage:

Drug	Dosage	Route	Frequency
All cycles			
Rituximab	**375mg/m^2**	IV infusion	Day 1 of a 21 day cycle
Polatuzumab vedotin	**1.8mg/kg (max 240mg)**	IV infusion	Day 1 of a 21 day cycle
Bendamustine	**90mg/m^2/day**	IV infusion	Days 1 and 2 of a 21 day cycle

Cycle frequency:

Every 21 days for a maximum of 6 cycles

Administration:

- If a planned dose of polatuzumab vedotin is missed, it should be administered as soon as possible and the schedule of administration should be adjusted to maintain a 21 day interval between doses.
- Patients will required irradiated blood products (lifelong) –the patients receive information booklets about irradiated blood when counselled by the specialist nurses. It contains an alert car that the patient carries around with them. The specialist nurses then contact the lab.
- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.
- Women of reproductive potential should be advised to use effective contraception during treatment with polatuzumab vedotin and for at least 9 months after the last dose.
- Male patients, with female partners of reproductive potential, should be advised to use effective contraception during treatment with polatuzumab vedotin and for at least 6months after the last dose.

Initial dose of polatuzumab vedotin is administered over 90 minutes. Subsequent infusions can be administered over 30minutes if the prior infusion was well tolerated Monitor observations as routine for the duration of each infusion and for 90 minutes following completion of the initial dose. Post dose observation time may be decreased to 30 minutes if the initial dose was well tolerated.

Emetogenic risk:

Moderately emetogenic.

Supportive treatments:

Pre rituximab infusion medication:

- Paracetamol tablet 1gram oral (PO)
- Chlorphenamine injection 10mg intravenous (IV)
- Ensure oral steroids have been taken at least 30 minutes prior to rituximab

Supportive medication:

- Ondansetron 8mg twice daily (BD) for 5 days
- Metoclopramide 10mg three times a day when required
- Allopurinol (dose based on renal function) for first two cycles
- Co-trimoxazole 480mg daily
- Aciclovir 400mg twice daily is not generally required but may be given at the discretion of the prescriber.

Extravasation risk:

- Polatuzumab vedotin: non-vesicant
- Rituximab: non-vesicant
- Bendamustine: vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Interactions:

No drug-drug interaction studies with polatuzumab vedotin in humans have been conducted. See summary of product characteristics for more information.

Bendamustine metabolism involves the CYP P450 1A2 pathway. There is potential for interaction with CYP1A2 inhibitors such as ciprofloxacin, aciclovir and cimetidine (concomitant use with these medications may slow down metabolism of bendamustine).

For more detailed interactions please refer to the SPC

Main toxicities:

Infusion related reactions, anaemia, thrombocytopenia, neutropenia, fatigue, diarrhoea, nausea, pyrexia and peripheral neuropathy

Treatment Schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Paracetamol**	1g	PO	At least 30 minutes before rituximab
	Chlorphenamine	10mg	IV	
	Hydrocortisone	100mg	IV	
	Rituximab	375mg/m^2	IV	**≤450mg** in 250mL 0.9% sodium chloride **≥500mg** in 500mL 0.9% sodium chloride Rate as per rituximab infusion guideline
	Polatuzumab vedotin	1.8mg/kg	IV	<80mg: 50mL sodium chloride 0.9% 80-279mg: 100mL sodium chloride 0.9% ≥280mg: 250mL sodium chloride 0.9% The initial dose of polatuzumab vedotin should be administered as a 90-minute intravenous infusion. Patients should be monitored for reactions during the infusion and for at least 90 minutes following completion of the initial dose. If the prior infusion was well tolerated, the subsequent dose of polatuzumab vedotin may be administered as a 30-minute infusion and patients should be monitored during the infusion and for at least 30 minutes after completion of the infusion. Polatuzumab vedotin should be administered as an intravenous infusion through a dedicated infusion line equipped with a sterile, non-pyrogenic, low-protein binding in-line or add-on filter (0.2 or 0.22 micrometer pore size) and catheter.
	Bendamustine	90mg/m^2	IV	500mL Sodium Chloride 0.9% over 60 minutes
2	**Bendamustine**	90mg/m^2	IV	500mL Sodium Chloride 0.9% over 60 minutes

Investigations and treatment plan:

	Pre	Cycle 1 Day 1	Cycle 1 Day 2	Cycle 2 Day 1	Cycle 2 Day 2	Cycle 3+ Day 1	Cycle 3+ Day 2	Ongoing
Clinical Assessment	X			X		X		As clinically indicated or at the end of treatment
SACT Assessment (including performance status and toxicity assessment)		X	X	X	X	X	X	Every cycle
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X							
FBC	X	X		X		X		Every cycle
U&E & LFTs & Bone profile	X	X		X		X		Every cycle
CrCl (Cockcroft and Gault)	X							Every cycle
PET CT scan	X							Repeat at the end of treatment
CT Scan								Interim scan after three cycles
Informed Consent	X							
Blood pressure	X	X		X		X		Continuous monitoring required if on rituximab/ polatuzumab vedotin *
Temperature, respiratory rate, pulse		X		X		X		Continuous monitoring required if on rituximab/ polatuzumab vedotin *
Weight	X	X		X		X		Every cycle
Height	X							
Pregnancy test	X							Where appropriate

Dose Modifications and Toxicity Management:

Haematological toxicity:

Neutropenia Grade 3-4**	First occurrence	Hold all treatment until ANC recovers to > 1 x10^9/L. If ANC recovers to > 1 x10^9/L on or before day 7, resume all treatment without any additional dose reductions. If ANC recovers to >1x10^9/L after day 7: • Restart all treatment with a dose reduction of bendamustine from 90mg/m^2 to 70mg/m^2
	Second occurrence	Hold all treatment until ANC recovers to > 1 x10^9/L. If ANC recovers to > 1 x10^9/L on or before day 7, resume all treatment without any additional dose reductions. If ANC recovers to >1x10^9/L after day 7: • Restart all treatment with a dose reduction of bendamustine from 70mg/m^2 to 50mg/m^2
	Third occurrence	Hold all treatment until ANC recovers to > 1 x10^9/L. If ANC recovers to > 1 x10^9/L on or before day 7, resume all treatment without any additional dose reductions. If ANC recovers to >1x10^9/L after day 7: • Discontinue all treatment
Thrombocytopenia Grade 3-4**	First occurrence	Hold all treatment until platelets recover to >75x10^9/L. If platelets recover to >75x10^9/L on or before day 7, resume all treatment without any dose reductions. If platelets recover to >75x10^9/L after day 7: • Restart all treatment with a dose reduction of bendamustine from 90mg/m^2 to 70mg/m^2
	Second occurrence	Hold all treatment until platelets recover to >75x10^9/L. If platelets recover to >75x10^9/L on or before day 7, resume all treatment without any dose reductions. If platelets recover to >75x10^9/L after day 7: • Restart all treatment with a dose reduction of bendamustine from 70mg/m^2 to 50mg/m^2
	Third occurrence	Hold all treatment until platelets recover to >75x10^9/L. If platelets recover to >75x10^9/L on or before day 7, resume all treatment without any dose reductions. If platelets recover to >75x10^9/L after day 7: • Discontinue all treatment

****If primary cause of myelosuppression is due to lymphoma, the dose of bendamustine may not need to be reduced. GCSF prophylaxis can be considered.**

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Polatuzumab vedotin		
Infusion Related Reactions	The infusion rate of polatuzumab vedotin should be slowed or interrupted if the patient develops an infusion- related reaction. Polatuzumab vedotin should be discontinued immediately and permanently if the patient experiences a life-threatening reaction.	
Peripheral Neuropathy	Grade 2-3	Hold polatuzumab vedotin until improvement to ≤Grade1. If recovered to grade ≤1 on or before day 14, restart polatuzumab vedotin at a permanently reduced dose of 1.4mg/kg. If a prior dose reduction to 1.4mg/kg has occurred, permanently discontinue polatuzumab vedotin If not recovered to grade ≤1 on or before day 14, discontinue polatuzumab vedotin
	Grade 4	Discontinue polatuzumab vedotin
Rituximab		
Cytokine release syndrome	Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalization of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case by case basis. Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms.	

Bendamustine	
Rash	If skin reactions are progressive, bendamustine hydrochloride should be withheld or discontinued. For severe skin reactions with suspected relationship to bendamustine hydrochloride, treatment should be discontinued.

Renal and Hepatic Dosing:

Polatuzumab vedotin		
Renal Impairment	No dose adjustments necessary for CrCl ≥30ml/min. There is limited data on the use of polatuzumab in patients with CrCl <30ml/min.	
Liver Impairment	Mild impairment (bilirubin <1.5xULN or AST >ULN)	No dose adjustment necessary
	Moderate or severe impairment (bilirubin >1.5xULN)	Avoid use
Rituximab		
Renal Impairment	No dose adjustment necessary	
Liver Impairment	No dose adjustment necessary	
Bendamustine		
Renal Impairment	On the basis of pharmacokinetic data, no dose adjustment is necessary in patients with a creatinine clearance of > 10 ml/min. Experience in patients with severe renal impairment is limited.	
Liver Impairment	Mild impairment (serum bilirubin <21micromol/L)	No dose adjustment necessary
	Moderate hepatic impairment (serum bilirubin 21-50micromol/L).	A 30% dose reduction is recommended
	Severe hepatic impairment (serum bilirubin >50micromol/L)	No data is available

References:

References:

1. eMC UK Summary of Product Characteristics for Rituximab, Napp Pharmaceuticals, 13-Oct-2020 (last accessed 12th November 2020)
2. eMC UK Summary of Product Characteristic for Bendamustine, Zentiva Pharmaceuticals, 10-Oct-2020 (last accessed 12th Nov 2020)
3. eMC UK Summary of Product Characteristics for Polatuzumab, Roche, 05-Mar-2020 (last accessed 12th November 2020)
4. Summary of Product Characteristics, Polivy 140mg powder for concentrate for solution for infusion. July 2022. Monograph available from: http://www.medicines.org.uk [accessed Sep 2022]
5. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20: e201–08.
6. Polarix trial. Tilly et al. N Engl J Med 2022; 386:351-63. DOI: 10.1056/NEJMoa2115304

Circulation/Dissemination

Date added into Q-Pulse	28th April 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
Dec 2020	V1	**David Breen – Pharmacist**	New protocol created – on old trust format
Feb 2023	V2	**Daniel Dutton - Pharmacist**	Protocol minor update: polatuzumab changed from glucose to sodium chloride. Polatuzumab dose range infusion volume added Protocol moved to new format