PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Rituximab-Polatuzumab-CHP Diffuse Large B Cell Lymphoma (DLBCL)

PROTOCOL REF: MPHADLBCL
(Version No. 2.0)

Approved for use in:

- It is approved for previously untreated intermediate-risk or high-risk CD20 positive DLBCL (IPI score between 2 and 5) and grade 3B CD20 positive follicular lymphoma
- Primary CNS lymphoma, primary cutaneous DLBCL, primary effusion lymphoma, primary mediastinal B cell lymphoma, Burkitt lymphoma and plasmablastic lymphoma are **not** included for treatment with this first line polatuzumab combination
- It is **not** approved in patients with known CNS involvement
- Patients must have an ECOG performance status of 0 to 2.

Blueteq registration is required

Dosage:

Drug	Dosage	Route	Frequency
All cycles			
Rituximab	375mg/m^2	IV	Day 1 only
Cyclophosphamide	750mg/m^2	IV	Day 1 only
Doxorubicin	50mg/m^2	IV	Day 1 only
Polatuzumab	1.8mg/kg	IV	Day 1 only
Prednisolone	100mg	PO	Once daily Days 1 to 5

Cycle frequency:

Every 21 days for a maximum of 6 cycles

Administration:

- 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.
- Doxorubicin may impart a red colour to the urine. Patients should be cautioned that this does not pose any health hazards.
- Polatuzumab, rituximab, cyclophosphamide and doxorubicin can be administered in any order on day 1 after the administration of prednisolone

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 for 5 days.
- Metoclopramide 10mg three times a day when required.
- Allopurinol (dose based on renal function) for the first cycle.
- Docusate Sodium 200mg twice daily when required
- Filgrastim (G-CSF, e.g. Zarzio) if required, as secondary prophylaxis. Dose is weight dependent. To start on day 5 and administer subcutaneously once daily for 5 days.
- Aciclovir 400mg BD and co-trimoxazole 480mg daily are not generally required but may be given at the discretion of the prescriber.

Extravasation risk:

- Rituximab: Non-vesicant
- Cyclophosphamide: Non-vesicant
- Doxorubicin: Vesicant
- Polatuzumab: Non-vesciant

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

Interactions:

Rituximab

No known interactions with rituximab

Cyclophosphamide

Cyclophosphamide is inactive, but is metabolised in the liver, mainly by CYP2A6, 2B6, 2C9, 2C19 and 3A4, into two active metabolites. There are a number of potential interactions – please see SPC for more details.

Doxorubicin

Phenytoin given with doxorubicin may reduce blood levels of the anticonvulsant and to increase seizure activity. Therapeutic Drug Monitoring (TDM) for phenytoin would be advised.

Concomitant administration of inhibitors of CYP450 and/or P-glycoprotein might lead to increased plasma concentrations of doxorubicin and thereby increased toxicity.

Clozapine may increase the risk/severity of the haematologic toxicity of doxorubicin

Doxorubicin may reduce oral bioavailability of digoxin.

Polatuzumab

Strong CYP3A4 and P-gp inhibitors (e.g., ketoconazole) may increase the plasma concentration of unconjugated MMAE (vedotin). Caution is advised in case of concomitant

treatment with strong CYP3A4 inhibitor (e.g., boceprevir, clarithromycin, cobicistat, indinavir, itraconazole, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole) and patients taking these medicines should be monitored more closely for signs of toxicities.

Strong CYP3A4 inducers (e.g., rifampicin, carbamazepine, phenobarbital, phenytoin, St John's wort [*Hypericum perforatum*]) may decrease the exposure of unconjugated MMAE and so lead to decreased efficacy.

For more detailed interactions please refer to the SPC

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, constipation, peripheral neuropathy, mucositis, haemorrhagic cystitis, infusion related reactions, fatigue and cardiotoxicity

Treatment Schedule:

Day	Drug	Dosage	Route	Diluent and Rate
1	Paracetamol	1g	PO	At least 30mins before rituximab
	Chlorphenamine	10mg	IV	
	Prednisolone	100mg	PO	
	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	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 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 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 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.
	Ondansetron	8mg	IV	Over 15 minutes
	Cyclophosphamide	750mg/m^2	IV	In 250mL Sodium Chloride 0.9% over 30 mins
	Doxorubicin	50mg/m^2	IV	In 100mL Sodium Chloride 0.9% over 30 mins
2 to 5	Prednisolone	100mg	PO	Mane

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X	X	X	X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
FBC	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle
Hepatitis B screen (surface antigen and core antibody) and Hep C and HIV 1 and 2	X				
CT or PET-CT scan	X				Interim and at the end of treatment and if clinically indicated
ECHO or MUGA Scan	X				Before treatment in patients over 60 or with pre-existing cardiac disease
ECG	X				If clinically indicated
Blood pressure measurement	X	X	X	X	Frequent monitoring required when on rituximab
Respiratory Rate, Temp, RR	X	X	X	X	Frequent monitoring required when on rituximab
Weight recorded	X	X	X	X	
Height recorded	X	X	X	X	

Dose Modifications and Toxicity Management:

Haematological toxicity:

Note: no dose modifications required for first cycle	
Neutrophils (x10^9/L)	**Modification**
<1 on day of treatment	Withhold all treatment until ANC recovers to ≥ 1x10^9/L If ANC recovers to ≥ 1x10^9/L on or before day 7, resume all treatment without any dose reductions. If ANC recovers to ≥ 1x10^9/L after day 7: resume all 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%. Consider GCSF with future cycles
Any febrile neutropenia following any cycle of R-P-CHP	All subsequent cycles should be given with GCSF support. Consider dose reduction.
Febrile neutropenic episode despite G-CSF support	Consider reduction of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Platelets (x10^9/L)	**Modification**
<50 on day of treatment	Withhold 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: resume all 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%.
Second delay due to thrombocytopenia	Consider reducing dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles

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.

<table>
<tr><th colspan="6">Dose Modifications</th></tr>
<tr><th></th><th colspan="2">Renal Impairment</th><th colspan="3">Hepatic Impairment</th></tr>
<tr><td>Rituximab</td><td colspan="2">No dose adjustment necessary</td><td colspan="3">No dose adjustment necessary</td></tr>
<tr><td rowspan="4">Cyclophosphamide</td><td>CrCl (ml/min)</td><td>Modification</td><td colspan="3" rowspan="4">Mild and moderate: no need for dose adjustment is expected.

Severe: not recommended due to risk of reduced efficacy</td></tr>
<tr><td>>30</td><td>100%</td></tr>
<tr><td>10-29</td><td>75%</td></tr>
<tr><td><10</td><td>Not recommended

If unavoidable consider 50% of the original dose</td></tr>
<tr><td rowspan="4">Doxorubicin</td><td colspan="2" rowspan="4">No dose adjustment necessary</td><td>Parameter</td><td colspan="2">Modification</td></tr>
<tr><td>Bilirubin 21-50 micromol/L</td><td colspan="2">50%</td></tr>
<tr><td>Bilirubin 51-85 micromol/L</td><td colspan="2">25%</td></tr>
<tr><td>Bilirubin >86 micromol/L or Child Pugh C</td><td colspan="2">Omit</td></tr>
<tr><td rowspan="3">Polatuzumab</td><td>CrCl (ml/min)</td><td>Modification</td><td>Parameter</td><td colspan="2">Modification</td></tr>
<tr><td>≥30</td><td>100%</td><td rowspan="2">Bilirubin > 32 micromol/L</td><td colspan="2" rowspan="2">Omit</td></tr>
<tr><td><30</td><td>No date available</td></tr>
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Non- Haematological toxicity:

Renal and Hepatic Dosing:

Infusion-related Reactions		
Rituximab	Severe infusion-related reactions with fatal outcome can have an onset ranging within 30 minutes to 2 hours after starting the first rituximab infusion. They can be characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome (TLS) in addition to fever, chills, rigors, hypotension, urticaria, and angioedema. Severe cytokine release syndrome may occur. 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 normalisation 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. Anaphylactic and other hypersensitivity reactions may occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion. 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	
Polatuzumab	Grade 1 to 3	Interrupt polatuzumab infusion and give supportive treatment. For the first instance of Grade 3 wheezing, bronchospasm, or generalized urticaria, permanently discontinue polatuzumab. For recurrent Grade 2 wheezing or urticaria, or for recurrence of any Grade 3 symptoms, permanently discontinue polatuzumab. Otherwise, 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 over 90 minutes. If no infusion-related reaction occurs, subsequent infusions may be

		administered over 30 minutes. Administer premedication for all cycles.
	Grade 4	Stop polatuzumab infusion immediately. Give supportive treatment. Permanently discontinue polatuzumab.

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

	Grade 3	**Sensory neuropathy:** • Withhold polatuzumab dosing until improvement to Grade ≤ 2. • Reduce polatuzumab to 1.4 mg/kg. • If already at 1.4 mg/kg, reduce polatuzumab to 1.0 mg/kg. If already at 1.0 mg/kg, discontinue polatuzumab. **Motor neuropathy:** • Withhold polatuzumab dosing until improvement to Grade ≤ 1. • Restart polatuzumab at the next cycle at 1.4 mg/kg. • If already at 1.4 mg/kg and Grade 2–3 occurs, withhold polatuzumab dosing until improvement to Grade ≤ 1. Restart polatuzumab at 1.0 mg/kg. • If already at 1.0 mg/kg and Grade 2–3 occurs, discontinue polatuzumab. If concurrent sensory and motor neuropathy, follow the most severe restriction recommendation above.
	Grade 4	Discontinue polatuzumab

References:

1. Summary of Product Characteristics, Truxima 500mg Concentrate for Solution for Infusion, Jan 2021. Monograph available from: http://www.medicines.org.uk [accessed Sep 2022].
2. Summary of Product Characteristics, Cyclophosphamide 500mg Powder for Solution for Injection or Infusion, March 2021. Monograph available from: http://www.medicines.org.uk [accessed on Sep 2022].
3. Summary of Product Characteristics, Doxorubicin 2mg/ml Concentrate for Solution for Infusion, May 2016. Monograph available from: http://www.medicines.org.uk [accessed Sep 2022].
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	20th April 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
Jan 2023	V1	**Aileen McCaughey – Pharmacist**	New protocol created
Feb 2023	V2	**Daniel Dutton - Pharmacist**	Protocol minor update: polatuzumab changed from glucose to sodium chloride. Polatuzumab dose range infusion volume added