PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

R – BAC
(RITUXIMAB, BENDAMUSTINE &CYTARABINE)
NON HODGKIN LYMPHOMA

PROTOCOL REF: MPHARBACHA
(Version No. 2.0)

Approved for use in:

- Relapsed or refractory Mantle Cell Lymphoma
- First line treatment of Mantle Cell Lymphoma in less fit patients unsuitable for more intensive treatment

Blueteq registration must be completed prior to initiation (bendamustine)

Dosage:

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV	Day 1 NB if the WCC is greater than 25x10^9/L then consider splitting 1st dose (Day 1: 100mg and Day 2: 375mg/m^2 minus 100mg)
Bendamustine	**70mg/m^2**	IV	Days 2 and 3 (once daily)
Cytarabine	**500mg/m^2 ****	IV	Days 2 to 4 (once daily)

**Dose can be increased to 800mg/m^2 if patient tolerates first cycle well – clinical decision.

Cycle length every 28 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 must employ effective contraceptive methods during and for 12 months after treatment with rituximab.
- 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 card that the patient carries around with them. The specialist nurses then contact the lab.

Emetogenic risk:

Severely emetogenic.

Supportive treatments:

Rituximab pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Hydrocortisone IV bolus 100mg

Bendamustine pre-infusion medicines:

- Ondansetron IV 8mg

Supportive medicines:

- Allopurinol oral 300mg once daily for first cycle. Consider rasburicase if high risk of tumour lysis syndrome.
- Aciclovir oral 400mg twice daily is not generally required but may be given at the discretion of the prescriber (if history of shingles)
- Chlorhexidine 0.2% mouthwash 10mls four times a day
- Co-trimoxazole PO 480mg once daily (continue for 3-6 months after treatment)
- Ondansetron oral 8mg twice daily for 7 days
- Metoclopramide oral 10mg three times daily when required
- Prednisolone 0.5% eye drops, 1 drop both eyes four times a day from days 2 to 7
- Consider filgrastim S/C once daily from day 7 for 7 days (300 micrograms if <70kg and 480 micrograms ≥70kg)

Extravasation risk:

Rituximab: non-vesicant

Bendamustine: vesicant

Cytarabine: non-vesicant

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

Interactions:

Rituximab – no significant interactions.

Bendamustine - concomitant use with CYP1A2 inhibitors such as ciprofloxacin, aciclovir and cimetidine may slow down metabolism of bendamustine. Cases of Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients who received bendamustine and allopurinol simultaneously.

Cytarabine - may reduce digoxin levels. Digoxin level monitoring is recommended.

An *in-vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. In patients on cytarabine being treated with gentamicin for a *K.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

For more detailed interactions please refer to the SPC.

Renal and Hepatic Dosing:

Renal Dose Modifications		
Bendamustine	< 10mL/min	Limited experience. Use with caution
	Hemodialysis	No dose adjustment is necessary
Cytarabine	No dose adjustments required	
Rituximab	No dose adjustments required	

Hepatic Dose Modifications		
Bendamustine	**Bilirubin (micromol/L)**	**Dose Modification**
	20 – 51	70% dose
	>51	Not recommended
Cytarabine	No dose adjustments required	
Rituximab	No dose adjustments required	

Treatment Schedule:

If lymphocytes <25x10^9/L prior to first dose and all subsequent doses:

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
2	**Ondansetron**	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	70mg/m^2	IV	500mL Sodium Chloride 0.9% over 60 minutes
	Cytarabine	500mg/m^2	IV	In 500mls sodium chloride 0.9% over 2 hours. Cytarabine must start 2 hours after completion of bendamustine.
3	**Ondansetron**	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	70mg/m^2	IV	500mL Sodium Chloride 0.9% over 60 minutes
	Cytarabine	500mg/m^2	IV	In 500mls sodium chloride 0.9% over 2 hours. Cytarabine must start 2 hours after completion of bendamustine.
4	**Ondansetron**	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Cytarabine	500mg/m^2	IV	In 500mls sodium chloride 0.9% over 2 hours. Cytarabine must start 2 hours after completion of bendamustine.

If lymphocytes ≥25x10^9/L prior to first dose then split rituximab dose as per table below:

Day	Drug	Dosage	Route	Diluent and Rate
1	**Paracetamol**	1g	PO	At least 30 minutes before rituximab
	Chlorphenamine	10mg	IV	
	Hydrocortisone	100mg	IV	
	Rituximab	100mg	IV	In 100mL sodium chloride 0.9% over 2 hours
2	**Paracetamol**	1g	PO	At least 30 minutes before rituximab
	Chlorphenamine	10mg	IV	
	Hydrocortisone	100mg	IV	

	Rituximab	375mg/m^2 minus 100mg	IV	**≤450mg** in 250mL 0.9% sodium chloride **≥500mg** in 500mL 0.9% sodium chloride Rate as per rituximab infusion guideline
3	**Ondansetron**	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	70mg/m^2	IV	500mL Sodium Chloride 0.9% over 60 minutes
	Cytarabine	500mg/m^2	IV	In 500mls sodium chloride 0.9% over 2 hours. Cytarabine must start 2 hours after completion of bendamustine.
4	**Ondansetron**	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	70mg/m^2	IV	500mL Sodium Chloride 0.9% over 60 minutes
	Cytarabine	500mg/m^2	IV	In 500mls sodium chloride 0.9% over 2 hours. Cytarabine must start 2 hours after completion of bendamustine.
5	**Ondansetron**	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Cytarabine	500mg/m^2	IV	In 500mls sodium chloride 0.9% over 2 hours. Cytarabine must start 2 hours after completion of bendamustine.

Main toxicities:

Bendamustine
Myelosuppression (dose might have to be titrated). Also: hypersensitivity, liver enzyme rise, cardiac disorders, nausea, vomiting, headache, alopecia, amenorrhea, anorexia, diarrhoea, constipation, mucositis, fatigue, possible risk of secondary malignancies, hepatitis B reactivation, non-melanoma skin cancer.
Cytarabine
Bone marrow suppression, nausea, diarrhoea, abdominal pain, oral ulceration, hepatic dysfunction, CNS, GI and pulmonary toxicity, reversible corneal toxicity, somnolence, convulsion, pulmonary oedema. A cytarabine syndrome is also recognized in which patients suffer from fever, myalgia, bone pain, occasional chest pains, maculopapular rash, conjunctivitis and malaise. It usually occurs 6 - 12 hours following administration. Neurotoxicity also reported, e.g. cerebellar damage.
Rituximab
Infusion related reactions, cytokine release syndrome. Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. Hepatitis B reactivation

Investigations and treatment plan:

	Pre	Cycle 1+ Day 1	Cycle 1+ Day 2	Cycle 1+ Day 3	Ongoing
Informed consent	X				
Clinical Assessment	X	X			As clinically indicated or at the end of treatment
SACT Assessment (including toxicity assessment and informed consent)		X	X	X	Every cycle
FBC, U&E & LFTs & Magnesium	X	X			Every cycle
CrCl (Cockcroft and Gault)	X				Every cycle
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X				
PET CT Scan	X				Repeat at end of treatment
CT Scan					Interim scan after 3 cycles
ECG					If clinically indicated
Blood pressure measurement	X	X			Continuous monitoring required while on rituximab
Temperature and Respiratory Rate		X			Continuous monitoring required while on rituximab
Height recorded	X				
Weight recorded	X	X			Every cycle
Pregnancy test	X				If clinically appropriate

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed on day 1 if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ or 100 x10^9/L

Delay for one week if cytopenias not disease related. Consider dose reductions, discuss with consultant.

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:

Infusion Related Reactions

Rituximab (IV)
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

Skin Reactions

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. Monitor closely for skin changes.

References:

1. https://www.medicines.org.uk/emc rituximab (accessed Sept 2023)
2. https://www.medicines.org.uk/emc bendamustine (accessed Sept 2023)
3. https://www.medicines.org.uk/emc cytarabine (accessed Sept 2023)
4. 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.
5. Lancashire and South Cumbria Cancer Network. R-BAC-800 chemotherapy regime. Thames Valley Strategic Clinical Network. RBAC protocol. Accessed Sept 2023.

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

Date	Version	Author name and designation	Summary of main changes
Dec 2020	V1.0	**Aileen McCaughey – HO Pharmacist**	New protocol
Oct 2023	V2.0	**Jennifer Gibson – Principal Pharmacist HO**	Transferred to new template. Rituximab infusion reaction information added. Ondansetron changed to IV. Split dose option added.