PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

RITUXIMAB AND BENDAMUSTINE
CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) & LOW GRADE NON HODGKIN LYMPHOMA

PROTOCOL REF: MPHARBCLHA
(Version No. 2.0)

Approved for use in:

Chronic Lymphocytic Leukaemia (CLL)

- The first-line treatment of CLL in patients for whom fludarabine combination chemotherapy is not appropriate.
- Patients with relapsed B-cell chronic lymphocytic leukaemia (B-CLL) who are not eligible for treatment with BTK or BCL2 inhibitors **(not routinely commissioned by NHSE)**

NB. BR has shown only limited efficacy in patients refractory to fludarabine or patients with TP53 deletions or mutations.

Blueteq is not required for CLL indications

Low Grade Lymphoma

- First line treatment of low grade lymphoma or mantle cell lymphoma **(off-label indications)**
- Treatment of relapsed low grade non-Hodgkin lymphoma who are unable to receive R-CHOP, FCR or other high dose therapy and has had no prior bendamustine **(off label indication)**

Blueteq registration must be completed prior to initiation for all low grade lymphoma indications

Dosage:

CLL (First line treatment)

Drug	Dose	Route	Frequency
Cycle 1			
Rituximab	**375mg/m^2**	IV infusion	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	**90mg/m^2**	IV infusion	Days 1 and 2
Cycle 2 to 6			
Rituximab	**500mg/m^2**	IV infusion	Day 1
Bendamustine	**90mg/m^2**	IV infusion	Days 1 and 2

Cycle length every 28 days, for a maximum of 6 cycles

CLL (Relapsed disease)

Drug	Dose	Route	Frequency
Cycle 1			
Rituximab	**375mg/m^2**	IV infusion	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 infusion	Days 1 and 2
Cycle 2 to 6			
Rituximab	**500mg/m^2**	IV infusion	Day 1
Bendamustine	**70mg/m^2**	IV infusion	Days 1 and 2

Cycle length every 28 days, for a maximum of 6 cycles

Lymphoma (First line or relapsed)

Drug	Dose	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1
Bendamustine	**90mg/m^2**	IV infusion	Days 1 and 2

Cycle length every 28 days, for a maximum of 6 cycles

Administration:

- Patients will require 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 will contact the lab to inform them of the need for irradiated blood products.
- 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.

Emetogenic risk:

Moderately 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 PO 300mg once daily for first cycle. Consider rasburicase if high risk of tumour lysis syndrome.
- Aciclovir PO 400mg twice daily is not generally required but may be given at the discretion of the prescriber.
- Ondansetron PO 8mg twice daily for 5 days
- Co-trimoxazole PO 480mg once daily (continue for 3-6 months after treatment)
- Metoclopramide PO 10mg three times daily when required

Extravasation risk:

- Rituximab: non-vesicant
- Bendamustine: 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.

For more detailed interactions please refer to the SPC.

Renal and Hepatic Dosing:

Renal Dose Modifications	
Rituximab	No adjustment necessary
Bendamustine	Limited experience. No dose adjustment is necessary in patients with a creatinine clearance of > 10 ml/min. Use with caution in severe impairment

Hepatic Dose Modifications		
Rituximab	No adjustment necessary	
Bendamustine	**Bilirubin (micromol/L)**	**Dose Modification**
	21 - 50	70% dose
	>50	No data available

Main toxicities:

Rituximab
Severe cytokine release syndrome is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, angioedema, and hepatitis B reactivation.
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.

Treatment Schedule:

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
	Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	See indication & cycle no.	IV	500mL Sodium Chloride 0.9% over 60 minutes
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
	Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	See indication & cycle no.	IV	500mL Sodium Chloride 0.9% over 60 minutes

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	See indication and cycle no.	IV	**≤450mg** in 250mL 0.9% sodium chloride **≥500mg** in 500mL 0.9% sodium chloride Rate as per rituximab infusion guideline
	Ondansetron	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	See indication & cycle no.	IV	500mL Sodium Chloride 0.9% over 60 minutes
2	**Ondansetron**	8mg	IV	In 100mL sodium chloride 0.9% over 15-30 minutes
	Bendamustine	See indication & cycle no.	IV	500mL Sodium Chloride 0.9% over 60 minutes

Investigations and treatment plan:

	Pre	Cycle 1, D1	Cycle 2+ D1	Ongoing
Informed Consent	X			
Clinical Assessment	X	X	X	Every cycle
SACT Assessment (including PS and toxicity assessment)		X	X	Every cycle
FBC	X	X	X	Every cycle
U&E & LFTs & Calcium profile	X	X	X	Every cycle
CrCl (Cockcroft and Gault)	X			Every cycle
CT scan and bone marrow biopsy	X			If clinically indicated
Blood pressure	X	X	X	Continuous monitoring required if on Rituximab
Temperature, respiratory rate, pulse		X	X	Continuous monitoring required if on Rituximab
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X			
Height	X			
Weight	X	X	X	Every cycle
Pregnancy test	X			Where appropriate

Dose Modifications and Toxicity Management:

Haematological toxicity:

No dose modification required for cycle 1.

Subsequent cycles to proceed if-

ANC ≥ 1.0 x 10^9/L	Platelets ≥ 50 x 10^9/L

If ANC < 1 x 10^9/L or platelets < 50 x 10^9/L then chemotherapy to be delayed until blood counts have increased above these values. Bendamustine is to be dose reduced to 50mg/m^2 for the first episode of cytopenia and reduced to 25mg/m^2 for subsequent episodes. No dose reduction for rituximab is required.

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:

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. Monitor closely for skin changes.

References:

1. eMC UK Summary of Product Characteristics for Rituximab (Truxima), updated 13-Dec-2022 (last accessed 4/7/23)
2. eMC UK Summary of Product Characteristic for Bendamustine, Zentiva Pharmaceuticals, 14-Oct-2021 (last accessed 4/7/23)
3. Bendamustine for first line treatment of CLL. NICE TA 216.February 2011.
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. Bendamustine and Rituximab for CLL. Thames Valley Strategic Clinical Network v3.1. May 2021.

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
June 2020	V1.0	**Aileen McCaughey – HO Pharmacist**	New protocol
July 2023	V2.0	**Jennifer Gibson – Principal Pharmacist HO**	Transferred to new template. Merged protocol for 1st line CLL, r/r CLL and low grade NHL.