SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

RITUXIMAB & CHLORAMBUCIL CHRONIC LYMPHOCYTIC LEUKAEMIA (CLL) & NON-HODGKIN LYMPHOMA (NHL)

PROTOCOL REF: MPHARICHHA
(Version No. 2.0)

Approved for use in:

- Treatment of CLL in elderly patients for whom treatment with fludarabine and cyclophosphamide (R-FC) or chlorambucil and obinutuzumab (O-Chlorambucil) or bendamustine (R-Bendamustine) is not considered appropriate, due to co-morbidities or performance status.
- Low grade NHL

Blueteq registration is not required.

Dosage:

Cycle 1

Drug	Dosage	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1
Chlorambucil	**10mg/m^2 *or* 10mg flat dose *or* 0.5mg/kg**	oral	Days 1 to 7 Days 1 to 7 Days 1 and 15

Cycle 2 to 12

Drug	Dosage	Route	Frequency
Rituximab	**375mg/m^2**	IV infusion	Day 1 **NHL ONLY**
	or		
	500mg/m^2	IV infusion	Day 1 **CLL ONLY**
Chlorambucil	**10mg/m^2 *or* 10mg flat dose *or* 0.5mg/kg**	oral	Days 1 to 7 Days 1 to 7 Days 1 and 15

Cycle length of 28 days. Maximum of 12 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.
- Chlorambucil needs to be kept in a fridge.
- Chlorambucil tablets should be taken daily on an empty stomach (at least one hour before meals or three hours after meals).
- Continued treatment with chlorambucil should be assessed if a rash develops since there have been reports of Stevens - Johnson syndrome in patients receiving chlorambucil.

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

Rituximab Pre-medication:

- Paracetamol orally 1g to be taken 30 minutes prior to the infusion
- Chlorphenamine intravenously 10mg to be taken 30 minutes prior to the infusion
- Hydrocortisone sodium succinate 100mg IV bolus

Take home medication:

- Allopurinol 300mg daily (reduce dose if renal dysfunction) for the first two cycles. Consider rasburicase if high risk (lymphocytes ≥25x10^9/L).
- Aciclovir 400mg twice daily
- Metoclopramide 10mg three times a day when required

Extravasation risk:

Rituximab– non vesicant

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

Dosing in renal and hepatic impairment:

Renal	Rituximab	No dose adjustments required
	Chlorambucil	Dose adjustment is not considered necessary in renal impaired patients.

Hepatic	Rituximab	No dose adjustments required
	Chlorambucil	Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity. Since chlorambucil is primarily metabolised in the liver, dose reduction should be considered in patients with severe hepatic impairment.

Interactions:

No known interactions with rituximab.

Avoid live vaccinations whilst taking chlorambucil. Other cytotoxic and chemotherapy agents should be avoided with chlorambucil due to increased risk of myelosuppression.

Treatment schedule:

If lymphocyte counts >25x10^9/L prior to cycle 1 should be considered for split dose rituximab cycle 1 (100mg day 1 then 375mg/m^2 minus 100mg given on day 2 if no IRR on day 1).

Day	Drug	Dose	Route	Diluent and rate
CYCLE 1 CLL / ALL CYCLES NHL				
1	**Hydrocortisone**	**100mg**	IV	To be administered 30 minutes prior to the infusion
	Paracetamol	**1000mg**	PO	To be administered 30 minutes prior to the infusion
	Chlorphenamine	**10mg**	IV	To be administered 30 minutes prior to the infusion
	Rituximab	***375mg/m^2**	IV	In 500mL sodium chloride 0.9%
	Chlorambucil	**See dose section**	PO	See dose section. Round to the nearest 2mg
CYCLE 2-6 CLL ONLY				

1	**Hydrocortisone**	**100mg**	IV	To be administered 30 minutes prior to the infusion
	Paracetamol	**1000mg**	PO	To be administered 30 minutes prior to the infusion
	Chlorphenamine	**10mg**	IV	To be administered 30 minutes prior to the infusion
	Rituximab	****500mg/m^2**	IV	In 500mL sodium chloride 0.9%
	Chlorambucil	**See dose section**	PO	See dose section. Round to the nearest 2mg

*In CLL patients, if lymphocyte count ≥25x10^9/L prior to cycle 1 then 100mg should be given on day 1 (in 100mL sodium chloride 0.9% over 2 hours at 50mL/hour) followed by 375mg/m^2 minus 100mg given on day (in 500mL sodium chloride 0.9%). Total dose of 375mg/m^2. Give pre-medications on both days.
**In CLL patients, providing no IRR with cycle 1 then dose can be escalated to 500mg/m^2. If IRR with cycle 1 consider maintaining dose of 375mg/m^2 and escalating if appropriate in subsequent cycles.

Rituximab Infusion Rates:

See Rituximab Administration Guideline.

Main toxicities:

Rituximab
Infusion related reactions; 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.
Chlorambucil
Leukopenia, neutropenia, thrombocytopenia, pancytopenia or bone marrow suppression Gastro-intestinal disorders such as nausea and vomiting, diarrhoea and mouth ulceration Rash - well recognized complication usually widespread maculo-papular. Monitor closely. Rare cases of Stevens-Johnson syndrome, or toxic epidermal necrolysis have been reported.

Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D2 (if split dose rituximab)	Cycle 2+ D1	Ongoing
Informed consent	X				
Clinical and SACT Assessment	X	X		X	Every cycle 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
Hepatitis B surface antigen, Hepatitis B core antibody, Hepatitis C antibody and HIV	X				
CT scan and bone marrow	X				If clinically indicated pre and post treatment
Blood pressure	X	X	X	X	Continuous monitoring required if on Rituximab
Temp, respiratory rate, pulse		X	X	X	Continuous monitoring required if on Rituximab
Height	X				
Weight	X	X		X	Every cycle
Pregnancy testing	X				If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity

Proceed with cycle 1 irrespective of cytopenias (if thought to be due to disease).

Proceed subsequent cycles when;

Platelets ≥ 75 x10^9/L	ANC ≥ 1.0 x10^9/L

Consider proceeding with 2nd and subsequent cycles if persistent cytopenias are believed to be secondary to underlying disease. G-CSF support can be used from cycle 1.
If ANC < 1.0 x 10^9/L and/or platelets < 75 x 10^9/L due to therapy then delay for one week and if counts have recovered then resume chemo at previous doses. If counts have not recovered at 2 weeks then resume chemo but reduce chlorambucil dose by 50% if clinically appropriate. Consider adding GCSF if needed.

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:

See section entitled 'Dosing in Renal and Hepatic Impairment'

Neurotoxicity

Convulsions including partial or general seizures have been seen in adults receiving therapeutic daily doses or high dose pulses of chlorambucil. Use caution in patients with a history of seizures.

Infusion Related Reactions

Non-Haematological toxicities:	
Rituximab	
Infusion-related Reactions	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

References:

1. https://www.medicines.org.uk/emc Rituximab (accessed July 2023)
2. https://www.medicines.org.uk/emc Chlorambucil (accessed July 2023)
3. https://www.medicines.org.uk/emc Obinutuzumab (accessed July 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.

Circulation/Dissemination

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

Version History

		Author name and designation	Summary of main changes
June 2020	1.0	**Aileen McCaughey- Advanced Pharmacist HO**	**New protocol**
Aug 2023	2.0	**Jennifer Gibson – Principal Pharmacist HO**	**Transferred to new template. CLL and NHL protocols merged. Added in Chlorambucil dosing from CLL 11 trial.**