SACT PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

RITUXIMAB & LENALIDOMIDE (R^2) RELAPSED FOLLICULAR LYMPHOMA

PROTOCOL REF: MPHASCRLHA
(Version No. 2.0)

Approved for use in:

Follicular Lymphoma (FL) grade 1 to 3A, in patients who have previously been treated with at least one prior line of therapy for FL and have not previously received lenalidomide.

Blueteq registration is required

Dosage:

Drug	Dose	Route	Frequency
Cycle 1			
Rituximab	**375mg/m^2**	IV	Day 1, 8, 15 and 22
Lenalidomide	**20mg**	Oral	Once daily on days 1 to 21
Cycle 2 to 5			
Rituximab	**375mg/m^2** or **1400mg**	*IV or Subcutaneous	Day 1
Lenalidomide	**20mg**	Oral	Once daily on days 1 to 21
Cycle 6 onwards			
Lenalidomide	**20mg**	Oral	Once daily on days 1 to 21

*****Patient must have received a full dose intravenous rituximab over 1 day during cycle 1 without hypersensitivity reactions, before being switched to the subcutaneous formulation.

Cycle length 28 days. Maximum 12 cycles (max 5 cycles of rituximab).

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.
- Reactivation of Hepatitis B can occur if rituximab is administered to people previously exposed to Hepatitis B. Virology screening including Hepatitis B Core Antibody and Surface Antigen should be carries out and confirmed as negative prior to administration of rituximab. Any positive or equivocal result should be discussed with Consultant.
- Infusion related reactions (IRR) are a common side effect of rituximab. The infusion rate should be titrated slowly during the first infusion and the patient monitored closely for signs of IRR. Ensure pre-medications administered prior to every dose of rituximab.
- Rituximab 1400 mg subcutaneous formulation should be administered over approximately 5 minutes. The hypodermic injection needle must only be attached to the syringe immediately prior to administration to avoid potential needle clogging. It should be injected subcutaneously into the abdominal wall and never into areas where the skin is red, bruised, tender, hard or areas where there are moles or scars.
- Lenalidomide capsules should be taken orally at about the same time on the scheduled days. The capsules should not be opened, broken or chewed. The capsules should be swallowed whole, preferably with water, either with or without food.
- If a lenalidomide dose is missed and <12hours late the missed dose should be taken. Missed doses >12hours should be omitted and the next dose taken as scheduled.
- The prescriber must inform male and female patients about the expected teratogenic risk and the strict pregnancy prevention measures as specified in the pregnancy prevention programme and provide patients with appropriate patient educational brochure and patient card.

Pregnancy Prevention Programme:

Due to the increased risk of birth defects associated fetal exposure to lenalidomide the following should be adhered to:

- A Treatment Initiation Form (TIF) must be completed prior to treatment initiation with lenalidomide
- A Prescription Authorisation Form (PAF) must be completed by the prescriber for each supply of lenalidomide. This must be approved by a pharmacist when verifying each prescription and confirmation of dispensing completed by the relevant dispensing pharmacy. Supply must be completed within 7 days of the prescription generation.
- A maximum of 3 months can be supplied for men or women of non-child bearing potential
- A maximum of 1 month can be supplied for women of child bearing potential. A negative pregnancy test must be confirmed within 3 days of prescription generation.

Emetogenic risk

Mildly emetogenic

Supportive treatments:

IV Rituximab pre-infusion medicines:

- Paracetamol oral 1g
- Chlorphenamine IV bolus 10mg
- Hydrocortisone sodium succinate IV bolus 100mg

SC Rituximab pre-injection medicines:

- Paracetamol oral 1g
- Chlorphenamine oral 4mg

Supportive medicines:

- Allopurinol oral 300mg once daily for first cycle. Consider rasburicase if high risk of tumour lysis syndrome (e.g. lymphocytes ≥25x10^9/L)
- Consider G-CSF support, frequency titrated to response, if neutropenia.
- VTE prophylaxis (for cycle 1 to 6 and continued at clinician discretion:
    - Dalteparin 5,000 units subcutaneous injection daily (or alternative prophylactic LMWH)
    - Therapeutic dose LMWH in high risk patients. Patients may continue previously established DOAC treatment or be switched to a LMWH.

- Aspirin 75mg daily (for those patients who decline LMWHs or for those deemed to be low risk on long term treatment)

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 Modifications		
Rituximab	No dose recommendation required	
Lenalidomide	**Creatinine Clearance (mL/min)**	**Dose Adjustment**
	30 – 60	10mg once daily*
	<30	No data. Consider 5mg once daily

* The dose may be escalated to 15 mg once daily after 2 cycles if patient is not responding to but is tolerating the treatment.

Hepatic Modifications	
Rituximab	No dose recommendation required
Lenalidomide	Lenalidomide has not formally been studied in patients with impaired hepatic function and there are no specific dose recommendations.

Interactions:

Rituximab: No significant drug interactions

Lenalidomide:

- Agents that may increase the risk of thrombosis, such as HRT should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.
- **Digoxin** – concomitant administration with lenalidomide increased plasma exposure of digoxin, monitoring of the digoxin concentration is advised during lenalidomide treatment.
- **Statins** – there is an increased risk of rhabdomyolysis when statins are administered with lenalidomide. Enhanced clinical and laboratory monitoring is warranted notably during the first weeks of treatment.

Treatment schedule:

If lymphocytes ≥25x10^9/L then consider splitting the first dose (100mg in 100mL sodium chloride 0.9% over 2 hours on day 1 and then the remainder of the dose in 500mL sodium chloride 0.9% as per standard infusion rates on day 2). If no IRR then subsequent doses can be given in one infusion.

Cycle 1:

Day	Drug	Dose	Route	Diluent and rate
1 to 21	**Lenalidomide**	**20mg**	**PO**	Once daily (Give as TTO)
1, 8, 15 & 22	**Paracetamol**	**1g**	**PO**	30 mins prior to rituximab
	Chlorphenamine	**10mg**	**IV**	Bolus dose over 3-5 minutes. 30 mins prior to rituximab
	Hydrocortisone	**100mg**	**IV**	Bolus dose over 3-5 minutes. 30 mins prior to rituximab
	Rituximab	**375mg/m²**	**IV**	**≤450mg** 250mL sodium chloride 0.9% **≥500mg** 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline.

Cycle 2 to 5:

Day	Drug	Dose	Route	Diluent and rate
1 to 21	**Lenalidomide**	**20mg**	**PO**	Once daily (Give as TTO)
1	**Paracetamol**	**1g**	**PO**	30 mins prior to rituximab
	Chlorphenamine	**4mg**	**PO**	30 mins prior to rituximab
	Rituximab	**1400mg**	**SC**	Slow IV bolus over 5 minutes. Observe patients for at least 15 minutes following rituximab subcutaneous administration.

Main toxicities:

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
Lenalidomide
Infection, neutropenia, anaemia, thrombocytopenia, MDS, hypokalaemia, peripheral neuropathy, dyspnoea, diarrhoea, nausea, vomiting, constipation, deranged liver function tests, rash, muscle spasms, fatigue

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Investigations and treatment plan:

	Pre	Cycle 1 D1	Cycle 1 D8	Cycle 1 D15	Cycle 1 D22	Cycles 2-5 D1	Cycle 6+ D1	Ongoing
Informed consent	x							
Clinical Assessment & SACT Assessment (including performance status and toxicity assessment)	x	x				x	x	Every cycle
FBC, U&E, LFTs and calcium profile	x	x				x	x	
CrCl (Cockcroft and Gault)	x							
Tumour Lysis Bloods	x	x	x	x	x			Weekly for the first cycle
PET CT scan (high grade and FL lymphoma)	x							Subsequent imaging at discretion of consultant
CT scan (other low grade lymphomas	x							
Blood pressure	x	x	x	x	x			Continuous monitoring required if on Rituximab infusion
Temperature, respiratory rate, pulse		x	x	x	x			Continuous monitoring required if on Rituximab infusion.
Hepatitis B core antibody and surface antigens & Hep C antibody & HIV 1+2 antigen and antibody	x							
Height	x							
Weight	x	x				x	x	
Pregnancy test	x					x	x	If clinically indicated. Repeat each cycle if of childbearing potential
Treatment Initiation Form	x							
Prescription authorisation form		x				x	x	With each prescription

Dose Modifications and Toxicity Management:

Haematological toxicity:

Proceed if:

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

Treatment may go ahead if cytopenias suspected to be due to lymphoma infiltration of the bone marrow.

Dose Reduction Steps	
Starting dose	20mg daily
Dose level 1	15mg daily
Dose level 2	10mg daily
Dose level 3	5mg daily
Dose level 4	2.5mg daily

Platelets (x10^9/L)	Neutrophils (x10^9/L)	Recommended course
Falls to < 50	Falls < 1.0 for at least 7 days **or** Falls to < 1.0 with associated fever (body temperature ≥ 38.5°C) **or** Falls to < 0.5	Interrupt lenalidomide treatment and conduct a FBC at least every 7 days
Returns to ≥ 50	Returns to ≥ 1.0	Resume at next lower dose level (dose level 1)
For each subsequent drop below 50	For each subsequent drop below 1.0 for at least 7 days **or** Drop to < 1.0 with associated fever (body temperature ≥ 38.5°C) **or** Drop to < 0.5	Interrupt lenalidomide treatment and conduct a FBC at least every 7 days
Returns to ≥ 50	Returns to ≥1.0	Resume lenalidomide at next lower dose level.

Consider GCSF to keep neutrophils >1.0 x10^9/L, titrate frequency as needed. Add GSCF at clinician discretion if neutropenia is the only toxicity at any dose level.

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'

Tumour flare reaction (TFR)

Approximately 10% of patients are at risk of tumour flare. In patients with grade 3 or 4 TFR, withhold treatment with lenalidomide. TFR can be managed with interruption of lenalidomide and nonsteroidal anti-inflammatory drugs as indicated. Some patients with require a short course of steroid therapy. Lenalidomide can be restarted if resolution to grade 1 or less. Discuss with consultant.

For other grade 3 or 4 toxicities judged to be related to lenalidomide, treatment should be stopped and only restarted at next lower dose level when toxicity has resolved to ≤ grade 2 depending on the physician's discretion.

Lenalidomide interruption or discontinuation should be considered for grade 2 or 3 skin rash. Lenalidomide must be discontinued for angioedema, grade 4 rash, exfoliative or bullous rash, or if Stevens-Johnson syndrome (SJS), toxic epidermal necrolysis (TEN) or Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS) is suspected and should not be resumed following discontinuation from these reactions.

Infusion Related Reactions

Non-Haematological toxicities:	
Rituximab (IV)	
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 Lenalidomide (accessed 1/8/2023)
2. https://www.medicines.org.uk/emc Rituximab Truximab (accessed 1/8/2023)
3. https://www.medicines.org.uk/emc Rituximab MabThera 1400mg (accessed 1/8/2023)
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. NICE TA627. Lenalidomide with rituximab for previously treated follicular lymphoma. 7th April 2020.

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
May 2021	1.0	**David Breen – Principal Pharmacist**	New protocol
Sept 2023	2.0	**Jennifer Gibson – Principal Pharmacist HO**	Transferred to new template. Re-named as standard R2 protocol. Removed compassionate use indications. Added PPP information. Added administration information. Added TFR information.