Chemotherapy Protocol

LYMPHOMA

LENALIDOMIDE-RITUXIMAB (IV)

There are multiple versions of this protocol in use. Please ensure you have the correct protocol for the relevant diagnosis.

Regimen

- Lymphoma – Lenalidomide-Rituximab (IV)

Indication

- Follicular Lymphoma
  - anti-CD20 antibody sensitive (responded to the last anti-CD20 antibody containing regimen and had progressive disease more than six months after completion of that anti-CD20 antibody containing regimen) or
  - anti-CD20 antibody resistant (failed to respond to the last anti-CD20 antibody-containing regimen or had progressive disease within six months of completion of that anti-CD20 antibody-containing regimen
  - the patient has had no previous treatment with lenalidomide
  - the patient will be treated with a maximum of twelve 4-weekly cycles of lenalidomide
  - lenalidomide is only to be used in combination with rituximab and that it is not to be used in combination with any other agents. Note: if rituximab has to be discontinued for toxicity, lenalidomide can be continued up to the maximum of 12 cycles
  - prior to cycle 1 the patient will receive tumour lysis syndrome prophylaxis (allopurinol, rasburicase or equivalent as per institutional guideline) and that the patient will be counselled as to be well orally hydrated during the 1st week of the 1st cycle or longer if clinically indicated.
  - the patient will have routine biochemistry tests performed weekly during cycle 1 and as clinically indicated and these results will be reviewed on day of testing to check for tumour lysis syndrome (TLS) and its consequences.
  - the patient will be treated for any Tumour Flare Reaction as set out in the Summary of Product Characteristics (SmPC) for lenalidomide.
  - that a formal medical review as to whether treatment with lenalidomide in combination with rituximab should continue or not will be scheduled to occur at least by the end of the first 8 weeks of treatment.

Toxicity

Drug	Adverse Effect
Lenalidomide	Peripheral neuropathy, pneumonia, infections, venous thrombotic events, respiratory dysfunction, rashes, hypokalaemia, hypomagnesaemia, hypocalcaemia, teratogenic risk, GI disturbances, flu-like symptoms.
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy, skin reactions

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- Tumour lysis screen weekly during 1st cycle, this should be reviewed on the day bloods are taken
- Perform a venous thromboembolism (VTE) risk assessment prior to starting treatment. Prescribe thromboprophylaxis for patients with additional risk factors.
- Consider monitoring serum immunoglobulin levels
- Check hepatitis B status before starting treatment with rituximab
- Calcium and magnesium levels at regular intervals throughout treatment
- Thyroid function tests at baseline and at regular intervals throughout treatment

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Dose modifications for haematological toxicity in the table below are for general guidance only. Always refer to the responsible consultant as any dose reductions or delays will be dependent on clinical circumstances and treatment intent. Low counts can be a consequence of bone marrow infiltration as well as drug toxicity.

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL (80g/L).

Lenalidomide

Neutrophils ($x10^9$/L)	Dose Modifications
1 or more	100%
Less than 1	1st Occurrence Delay until recovery has occurred. Restart at full dose. 2nd Occurrence Delay until recovery has occurred. Restart at a dose of 15mg 3rd Occurrence Delay until recovery has occurred. Restart at a dose of 10mg 3rd Occurrence Delay until recovery has occurred. Restart at a dose of 5mg
Platelets ($x10^9$/L)	**Dose Modifications**
50 or more	100%
Less than 50	1st Occurrence Delay until recovery has occurred. Restart at a dose of 15mg 2nd Occurrence Delay until recovery has occurred. Restart at a dose of 10mg 3rd Occurrence Delay until recovery has occurred. Restart at a dose of 5mg

Hepatic Impairment

Drug	Bilirubin µmol/L		AST/ALT units/L	Dose (% of original dose)
Lenalidomide				No dose adjustments needed
Rituximab	N/A		N/A	No dose adjustment needed

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Lenalidomide	Greater than 50	100%
	30-50	Start treatment with 10mg once a day Lenalidomide dose can be increased to 15mg after 2 cycles if patient shows no response.
	Less than 30	Start treatment with 15mg on alternate days
	Less than 30 and requiring dialysis	5 mg once a day. On dialysis days, the dose should be administered following dialysis.
Rituximab	N/A	No dose adjustment needed

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Lenalidomide

Lenalidomide may be continued (maintain dose) in patients with laboratory TLS or NCI-CTC grade 1 clinical TLS, or at the physician's discretion, reduce dose by one level and continue lenalidomide. Vigorous intravenous hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy may be needed to reduce hyperuricaemia. Hospitalisation of the patient will be at physician's discretion.

In patients with Grade 2 to 4 clinical TLS, interrupt lenalidomide and obtain a chemistry panel weekly or as clinically indicated. Vigorous intravenous hydration should be provided and appropriate medical management according to the local standard of care, until correction of electrolyte abnormalities. Rasburicase therapy and hospitalisation will be at physician's discretion. When the TLS resolves to Grade 0, restart lenalidomide at next lower dose per physician's discretion

In general for all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. Reduce the daily dose to 15mg. On subsequent occurrences delay until recovery the dose may then be reduced to 10mg and 5mg consecutively. If a dose of 5mg is not tolerated treatment should be stopped.

Allergic or hypersensitivity reactions that occur at NCI-CTC grade 2, withhold treatment until the symptoms have resolved to NCI-CTC grade 1 or below. Treatment may be cautiously restarted at a daily dose of 15mg. For NCI-CTC grade 3 or above reactions discontinue the lenalidomide.

Lenalidomide should be discontinued if a desquamating rash of NCI-CTC grade 3 or above or NCI-CTC grade 4 non-desquamating rash develops.

Where a venous thrombosis or embolism develops at NCI-CTC grade 3 or above, stop treatment and start anticoagulation. Lenalidomide may be reinstated at the clinician’s discretion.

Rituximab

Infusion related adverse reactions have been observed in 10% of patients treated with rituximab.

Rituximab administration is associated with the onset of cytokine release syndrome. This condition is characterised by severe dyspnoea, often accompanied by bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria, and angioedema. It may be associated with some features of tumour lysis syndrome such as hyperuricaemia, hyperkalaemia, hypocalcaemia, acute renal failure, elevated lactate dehydrogenase (LDH) and can lead to acute respiratory failure and death. This effect on the lungs may be accompanied by events such as pulmonary interstitial infiltration or oedema, visible on a chest x-ray.

Cytokine release syndrome frequently occurs within one or two hours of initiating the first infusion.

Hypersensitivity reactions, including anaphylaxis, have been reported following the intravenous administration of proteins. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes of starting the infusion. Medicinal products for the treatment of allergic reactions should be available for immediate use in the event of hypersensitivity developing during the administration of rituximab.

Use of rituximab maybe associated with an increased risk of progressive multifocal leukoencephalopathy (PML). Patients must be monitored at regular intervals for any new or worsening neurological, cognitive or psychiatric symptoms that may be suggestive of PML. If PML is suspected, further dosing must be suspended until PML has been excluded. If PML is confirmed the rituximab must be permanently discontinued.

The presence of a viral upper respiratory tract infection at the time of treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment

Regimen

28 day cycle for 12 cycles

Cycle 1

Drug	Dose	Days	Administration
Lenalidomide	20mg	1-21 incl.	Oral
Rituximab	375mg/m^2	1,8,15,22	Intravenous infusion in 500ml sodium chloride 0.9%

Cycles 2, 3, 4, 5

Drug	Dose	Days	Administration
Lenalidomide	20mg	1-21 incl.	Oral
Rituximab	375mg/m^2	day 1	Intravenous infusion in 500ml sodium chloride 0.9%

Cycles 6, 7, 8, 9, 10, 11, 12

Drug	Dose	Days	Administration
Lenalidomide	20mg	1-21 incl.	Oral

Dose Information

- Lenalidomide is available as 20mg, 15mg, 10mg, 7.5mg, 5mg and 2.5mg capsules
- Rituximab (intravenous) will be dose rounded to the nearest 100mg (up if halfway)

Administration Information

Extravasation

- Rituximab – neutral

Other

- Lenalidomide should be swallowed whole, preferably with water, either with or without food at about the same time each day. The capsules should not be opened, broken or chewed. If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day

- The rate of administration of rituximab (intravenous) varies. Please refer to the rituximab administration guidelines

Additional Therapy

- Antiemetics

    - metoclopramide 10mg three times a day when required oral

- Allopurinol 300mg once a day for 7 days cycle one only in patients at risk of tumour lysis syndrome

- Adequate hydration in view of potential for tumour lysis syndrome

- Thromboprophylaxis in patients with additional risk factors for VTE

- Rituximab (intravenous) pre medication

  30 minutes prior to rituximab

    - chlorphenamine 10mg intravenous

    - hydrocortisone 100mg intravenous

    - paracetamol 1000mg oral

- Rituximab infusion reactions

    - hydrocortisone 100mg intravenous bolus when required for rituximab infusion related reactions
    - salbutamol 2.5mg nebule when required for rituximab related bronchospasm
    - consider pethidine 25-50mg intravenous bolus for rituximab related rigors that fail to respond to steroids.

Additional Information

- Patient, prescriber and pharmacy must comply with the pregnancy prevention programme.
- The National Patient Safety Agency alert NPSA/2008/RRR001 must be followed when prescribing, dispensing or administering oral chemotherapy.
- It must be made clear to all staff, including those in the community, that this is a short course of oral chemotherapy that must not be continued.
- Patients should be assessed for suitability for oral chemotherapy prior to starting treatment.

References
1. John P. Leonard, MD; Marek Trneny, MD; Koji Izutsu, MD; Nathan H. Fowler, MD; Xiaonan Hong, MD; Jun Zhu, PhD;Huilai Zhang, MD7; Fritz Offner, MD, PhD; Adriana Scheliga, MD; Grzegorz S. Nowakowski, MD; Antonio Pinto, MD;Francesca Re, MD; Laura Maria Fogliatto, MD, PhD; Phillip Scheinberg, MD; Ian W. Flinn, MD, PhD; Claudia Moreira, MD; Jos´e Cabeçadas, MD; David Liu, MD, PhD; Stacey Kalambakas, MD; Pierre Fustier, PhD19; Chengqing Wu, PhD; and John G. Gribben, MD, DSc; for the AUGMENT Trial Investigators. 2019. J Clin Oncol 37:1188-1199.
2. Revlimid® (lenalidomide) 25mg capules. eMC UK Summary of Product Characteristics for Revlimid 25mg, Celgene, 8 January 2020
3. UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009).
4. UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009).

REGIMEN SUMMARY

Lenalidomide-Rituximab (intravenous)

Cycle 1 Day 1, 8, 15, 22

1. Chlorphenamine 10mg intravenous
2. Hydrocortisone 100mg intravenous
3. Paracetamol 1000mg oral
4. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
5. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
6. Salbutamol 2.5mg nebule once only when required for the relief of rituximab infusion related reactions

Take Home Medicines (day 1 only)

7. Warning – Pregnancy Prevention Programme
   Administration Instructions
   Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.
8. Lenalidomide 20mg once a day for 21 days oral
   Administration Instructions
   Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

   Oral SACT

   Available as 20mg, 15mg, 10mg, 7.5mg, 5mg and 2.5mg capsules, please ensure dose modifications occur in multiples of these strengths.

   Swallow whole, not chewed with plenty of water.
9. Metoclopramide 10mg three times a day when required oral*

*The metoclopramide will be supplied on cycle one only. Thereafter it can be added from supportive treatments if further supplies are required.

Cycles 2, 3, 4, 5

Day One

10. Chlorphenamine 10mg intravenous
11. Hydrocortisone 100mg intravenous
12. Paracetamol 1000mg oral
13. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

14. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions

15. Salbutamol 2.5mg nebule once only when required for the relief of rituximab infusion related reactions

Take Home Medicines

16. Warning – Pregnancy Prevention Programme
    Administration Instructions
    Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

17. Lenalidomide 20mg once a day for 21 days oral
    Administration Instructions
    Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

    Oral SACT.

    Available as 20mg, 15mg, 10mg, 7.5mg, 5mg and 2.5mg capsules, please ensure dose modifications occur in multiples of these strengths.

    Swallow whole, not chewed with plenty of water.

Cycle 6, 7, 8, 9, 10, 11, 12

Take Home Medicines

18. Warning – Pregnancy Prevention Programme
    Administration Instructions
    Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

19. Lenalidomide 20mg once a day for 21 days oral
    Administration Instructions
    Lenalidomide is associated with a pregnancy prevention programme. Please ensure this is completed for all patients.

    Oral chemotherapy.

    Available as 20mg, 15mg, 10mg, 7.5mg, 5mg and 2.5mg capsules, please ensure dose modifications occur in multiples of these strengths.

    Swallow whole, not chewed with plenty of water.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	April 2020	None	Nanda Basker Haematology Pharmacist	Dr Rob Lown Consultant Medical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors that occur as a result of following these guidelines.