Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE-PREDNISOLONE-RITUXIMAB (R-CP)

Regimen

- Lymphoma – R-CP (21)-Cyclophosphamide-Prednisolone-Rituximab

Indication

- Lymphoplasmacytic lymphoma/Waldenstrom's macroglobulinaemia

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances, myelosuppression, neutropenia, leukopenia, mucositis, alopecia, fever
Prednisolone	Weight gain, gastro-intestinal disturbances, hyperglycaemia, infection, Cushing-like symptoms, hypokalaemia, sodium retention, osteoporosis, impaired wound healing, muscular atrophy, osteoporosis,
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy, neutropenia, infusion related reactions, angioedema, nausea, pruritus, rash, alopecia, fever, chills, asthenia, headache, decreased IgG levels.

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
- Check hepatitis B status before starting rituximab

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and limited drug specific toxicities. 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.

Dose modifications based on haematological parameters apply to cyclophosphamide.

Neutrophils ($x10^9$/L)	Platelets ($x10^9$/L)	Dose Modifications
More than or equal to 1.5	More than or equal to 100	Continue with treatment at 100%
1.0-1.49	More than or equal to 100	Reduce dose of cyclophosphamide To 75%
0.5-1.0 and/or	50-100	Reduce cyclophosphamide to 50%
Less than 0.5 and/or	Less than 50	Omit cyclophosphamide

Prednisolone and rituximab do not require dose modifications based on haematological parameters.

Hepatic Impairment

Please note that the approach may be different where abnormal liver function tests are due to disease involvement.

Drug	Bilirubin (µmol/L)		AST/ALT (units)	Dose (%of original dose)
Cyclophosphamide	more than 30		2-3xULN	Clinical decision. Evidence that exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary. There may be decreased efficacy in severe hepatic impairment.

Rituximab	N/A		N/A	No dose adjustment needed

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide	more than 20	100%
	10-20	75%
	less than 10	50%
Rituximab	N/A	No dose adjustment needed

*Consider mesna in patients with pre-existing bladder disorders. Give an oral dose of 40% of the cyclophosphamide dose (rounded upwards to the nearest 400mg) at 0, 2 and 6 hours after the administration of the cyclophosphamide.

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.

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

21 day cycle for 6 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	750mg/m^2	1	Intravenous bolus over 10 minutes
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%
Prednisolone	40mg/m^2	1,2,3,4,5	Oral

Dose Information

- Cyclophosphamide will be dose banded in accordance with the national dose bands (20mg/ml)
- Prednisolone tablets will be rounded to the nearest 5mg (up if half way)
- Rituximab will be dose rounded to the nearest 100mg (up if half way)

Administration Information

Extravasation

- Cyclophosphamide – neutral
- Rituximab – neutral

Other

- Prednisolone should be taken in the morning with or after food. Administration of prednisolone begins on the morning of chemotherapy.
- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

Additional Therapy

- Antiemetics

15-30 minutes prior to chemotherapy

- ondansetron 8mg oral or intravenous bolus

As take home medication

- metoclopramide 10mg three times a day when required oral
- ondansetron 8mg twice a day for 3 days oral

- Rituximab pre-medication

30 minutes prior to rituximab

- chlorphenamine 10mg intravenous bolus
- paracetamol 1000mg oral

On the morning of treatment

- prednisolone 40mg/m^2 oral to be self administered by the patient on the morning of treatment and for four days after rituximab treatment (this is part of the chemotherapy schedule as well as rituximab pre-medication)

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.

- Allopurinol 300mg once a day for 7 days oral for the first cycle only

- Consider anti-infective prophylaxis in high risk patients, including:

  - aciclovir 400mg twice a day oral
  - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only

- Growth factor according to local formulary choice. For example:

  - filgrastim or bioequivalent 300microgram once a day for 7 days from day 6 subcutaneous
  - lenograstim or bioequivalent 263microgram once a day for 7 days from day 6 subcutaneous
  - pegfilgrastim or bioequivalent 6mg **once only** on day 2 subcutaneous

- Mouthcare for the prophylaxis or treatment of mucositis in accordance with local guidelines

- Gastric protection with a proton pump inhibitor or a H2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

References

1. Sandoz Limited (2021). Cyclophosphamide 1000mg powder for solution for injection or infusion summary for product characteristic. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.
2. Roche products limited (2021). MabThera 100mg Concentrate for Solution for Infusion summary for product characteristics. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.
3. Accord-UK Ltd (2021). Prednisolone 25mg tablets summary of product characteristics. Available from https://www.medicines.org.uk/emc. Accessed 04/07/2022.

4. . Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, Zervas K, Tsatalas C, Kokkinis G, Repoussis P, Symeonidis A, Delimpasi S, Katodritou E, Vervessou E, Michali E, Pouli A, Gika D, Vassou A, Terpos E, Anagnostopoulos N, Economopoulos T, Pangalis G. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol. 2007 Aug 1;25(22):3344-9.
5. Gertz MA. Waldenström Macroglobulinemia: 2012 update on diagnosis, risk stratification, and management. Am J Hematol. 2012 May;87(5):503-10.
6. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and related disorders: IWWM-7 consensus Blood 2014 124:1404-1411

REGIMEN SUMMARY

R-CP -Cyclophosphamide-Prednisolone-Rituximab

Cycle 1

1. Warning – Check patient has taken the prednisolone dose
   Administration instructions:
   Please check the patient has taken prednisolone 100mg on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone dose oral 30 minutes prior to rituximab infusion.

2. Chlorphenamine 10mg intravenous bolus
   Administration instructions:
   Administer 30 minutes prior to rituximab infusion

3. Paracetamol 1000mg oral
   Administration instructions:
   Administer 30 minutes prior to rituximab infusion

4. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

5. Ondansetron 8mg oral or intravenous injection
   Administration Instructions
   May be given as 8mg intravenous injection if the oral route is not appropriate

6. Cyclophosphamide 750mg/ m^2 intravenous bolus over 10 minutes

7. Hydrocortisone 100mg intravenous bolus once only when required for the relief of rituximab related reactions
   Administration Instructions
   Hydrocortisone 100mg to be administered when required for the relief of rituximab infusion related reactions

8. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm
   Administration Instructions
   Salbutamol 2.5mg nebule to be administered when required for the relief of rituximab infusion related reactions

Take Home Medicines

9. Prednisolone 40mg/ m^2 once a day on the morning of the next treatment
   Administration instructions:
   Take the prescribed dose on the morning of day 1 of the cycle. This is the supply for your next cycle.
   The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

10. Prednisolone 40mg/ m^2 once a day for 4 days oral starting on day 2 of the cycle
    Administration instructions:
    Take the prescribed dose in the morning for four days starting on day 2 of the cycle.
    The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

11. Metoclopramide 10mg three times a day when required oral
    Administration instructions:
    Please dispense 28 tablets or nearest equivalent pack size

12. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment
    Administration Instructions
    Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

13. Allopurinol 300mg once a day oral for 7 days

14. Growth factor according to local formulary choice.
    Administration Instructions
    Dispense according to local formulary choice. For example:
    - filgrastim or bioequivalent 300microgram once a day for 7 days from day 6 subcutaneous
    - lenograstim or bioequivalent 263microgram once a day for 7 days from day 6 subcutaneous
    - pegfilgrastim or bioequivalent 6mg **once only** on day 2 subcutaneous

Cycles 2, 3, 4 and 5

15. Warning – Check patient has taken the prednisolone dose
    Administration instructions:
    Please check the patient has taken prednisolone 100mg on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone 100mg oral 30 minutes prior to rituximab infusion.

16. Chlorphenamine 10mg intravenous bolus
    Administration instructions:
    Administer 30 minutes prior to rituximab infusion

17. Paracetamol 1000mg oral
    Administration instructions:
    Administer 30 minutes prior to rituximab infusion

18. Rituximab 375mg/ m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

19. Ondansetron 8mg oral or intravenous injection
    Administration Instructions
    May be given as 8mg intravenous injection if the oral route is not appropriate

20. Cyclophosphamide 750mg/ m^2 intravenous bolus over 10 minutes

21. Hydrocortisone 100mg intravenous bolus once only when required for the relief of rituximab infusion related reactions
    Administration Instructions
    Hydrocortisone 100mg to be administered when required for the relief of rituximab infusion related reactions

22. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related Bronchospasm
    Administration Instructions
    Salbutamol 2.5mg nebule to be administered when required for the relief of rituximab infusion related reactions

Take Home Medicines

23. Prednisolone 40mg/ m^2 once a day on the morning of the next treatment
    Administration instructions:
    Take the prescribed dose on the morning of day 1 of the cycle. This is the supply for your next cycle.
    The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

24. Prednisolone 40mg/ m^2 once a day for 4 days starting on day 2 oral
    Administration instructions:
    Take the prescribed dose in the morning for four days starting on day 2 of the cycle.
    The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

25. Metoclopramide 10mg three times a day when required oral
    Administration instructions:
    Please dispense 28 tablets or nearest equivalent pack size

26. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of

treatment
Administration Instructions
Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

27. Growth factor according to local formulary choice. For example:
Administration Instructions
Dispense according to local formulary choice. For example:
- filgrastim or bioequivalent 300microgram once a day for 7 days from day 6 subcutaneous
- lenograstim or bioequivalent 263microgram once a day for 7 days from day 6 subcutaneous
- pegfilgrastim or bioequivalent 6mg **once only** on day 2 subcutaneous

Cycle 6

28. Warning – Check patient has taken the prednisolone dose
Administration instructions:
Please check the patient has taken prednisolone on the morning of rituximab administration. On occasions where individuals attend for treatment and have forgotten to take the prednisolone please administer prednisolone 100mg oral 30 minutes prior to rituximab infusion.

29. Chlorphenamine 10mg intravenous bolus
Administration instructions:
Administer 30 minutes prior to rituximab infusion

30. Paracetamol 1000mg oral
Administration instructions:
Administer 30 minutes prior to rituximab infusion

31. Rituximab 375mg/ m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

32. Ondansetron 8mg oral or intravenous injection
Administration Instructions
May be given as 8mg intravenous injection if the oral route is not appropriate

33. Cyclophosphamide 750mg/ m^2 intravenous bolus over 10 minutes

34. Hydrocortisone 100mg intravenous bolus once only when required for the relief of rituximab infusion related reactions
Administration Instructions
Hydrocortisone 100mg to be administered when required for the relief of rituximab infusion related reactions

35. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related Bronchospasm
Administration Instructions
Salbutamol 2.5mg nebule to be administered when required for the relief of rituximab infusion related reactions

Take Home Medicines

36. Prednisolone 40mg/ m^2 once a day for 4 days starting on day 2 of the cycle oral
Administration instructions:
Take the prescribed dose in the morning for four days starting on day 2 of the cycle.
The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference.

37. Metoclopramide 10mg three times a day when required oral
Administration instructions:
Please dispense 28 tablets or nearest equivalent pack size

38. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment
Administration Instructions

Take 8mg twice a day for three days starting on the evening of day 1 of the cycle

39. Growth factor according to local formulary choice. For example:

Administration Instructions

Dispense according to local formulary choice. For example:

- filgrastim or bioequivalent 300microgram once a day for 7 days from day 6 subcutaneous
- lenograstim or bioequivalent 263microgram once a day for 7 days from day 6 subcutaneous
- pegfilgrastim or bioequivalent 6mg **once only** on day 2 subcutaneous

DOCUMENT CONTROL

Version	Date	Amendment	Written by	Approved by
1	September 2022		Alexandra Pritchard Pharmacist	Dr Rob Lown Consultant

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 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. These protocols should be used in conjunction with other references such as the summary of product characteristics and relevant published papers.