Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE - DEXAMETHASONE – RITUXIMAB

(DRC)

Regimen

- Lymphoma – DRC – Cyclophosphamide – Dexamethasone - Rituximab

Indication

- Lymphophlasmacytic lymphoma / Waldenstrom's macroglobinaemia

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Dexamethasone	Weight gain, gastrointestinal disturbances, hyperglycaemia, CNS disturbances, Cushingoid changes, glucose intolerance.
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy

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 treatment with rituximab
- Regular monitoring of blood glucose is considered good practice.

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. Blood transfusion carries higher risk of TACO (transfusion associated circulatory overload) and thrombosis related to the height of the IgM paraprotein. Red blood cell transfusion decisions will always be individual to each patient and must be made by a consultant.

Dose modifications based on haematological parameters apply to cyclophosphamide only.

Neutrophils ($x10^9$/L)	**Dose Modifications (cyclophosphamide)**
Less than 1 on proposed day 1 of cycle	Delay therapy until neutrophils are greater than or equal to $1x10^9$/L Consider G-CSF as secondary prophylaxis. Reconsider treatment options if not recovered after 14 days.
Grade 4 neutropenia or any febrile neutropenia following any cycle	Give G-CSF with all subsequent cycles
Grade 4 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide by 50% for all subsequent cycles
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide	Stop treatment
Platelets ($x10^9$/L)	**Dose Modifications (cyclophosphamide)**
Less than 100 on proposed day 1 of cycle	Delay therapy until platelets are greater or equal to $100x10^9$/L Reconsider treatment options if not recovered after 14 days.
Grade 4 thrombocytopenia following any cycle	Reduce dose of cyclophosphamide by 50% for all subsequent cycles
Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide	Stop treatment

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/L)	Dose (%of original dose)
Cyclophosphamide	Evidence suggests dose modification not necessary.		
Rituximab	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

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.

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. The dose should then be reduced to 75% of the original dose or discontinued as appropriate.

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

3 week cycle for 8 cycles

Cycle 1

Drug	Dose	Days	Administration
Cyclophosphamide	100mg/m^2 twice a day	1, 2, 3, 4, 5	Oral (total dose 1000mg/m^2)
Dexamethasone	20mg once a day (iv dose equivalent)	1	Intravenous bolus*
Rituximab	100mg	1	Intravenous infusion in 50ml sodium chloride 0.9% over 120 minutes **
Rituximab	325mg/m^2	2	Intravenous infusion in 500ml sodium chloride 0.9% Omit rituximab if total IgM is more than 40g/l

Cycle 2 onwards

Drug	Dose	Days	Administration
Cyclophosphamide	100mg/m^2 twice a day	1, 2, 3, 4, 5	Oral (total dose 1000mg/m^2)
Dexamethasone	20mg once a day (iv dose equivalent)	1	Intravenous bolus*
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%**

*Dexamethasone needs to be prescribed orally if rituximab is omitted
**Omit rituximab if total IgM is more than 40g/l. Split dose of rituximab if total IgM more than 20g/l. If total IgM less than 20g/l give 375mg/m^2 in 500ml sodium chloride 0.9% on day 1

Dose Information

- Rituximab dose will be rounded to the nearest 100mg (up if halfway)
- Cyclophosphamide available as 50mg tablets. Dose will be rounded to nearest 50mg (up if half way).

Administration Information

Extravasation

- Rituximab - neutral

Other

- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines
- Dexamethasone is being used as part of the chemotherapy combination regimen – if rituximab is omitted the dexamethasone 20mg dose for day 1 needs to be prescribed orally
- Cyclophosphamide tablets should be swallowed whole with a full glass of water
- Cyclophosphamide may irritate the bladder mucosa. Patients should be encouraged to drink a minimum of three litres of fluid per 24hours
- Plasma exchange prior to each cycle should be considered if total IgM is more than 40g/l or there are clinical signs of hyperviscosity
- Start rituximab when IgM is less than 40g/l
- Split first dose of rituximab when total IgM is more than 20g/l as on cycle 1: 100mg in 50ml sodium chloride 0.9% over 2 hours on day 1 and 325mg/m^2 in 500ml sodium chloride 0.9% as per administration guidelines on day 2

Additional Therapy

- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral
  - hydrocortisone 100mg intravenous (if dexamethasone is not given i.e. day 2 split dose rituximab)

- Rituximab infusion reactions

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

- Allopurinol 300mg once a day oral until bulk disease is reduced (preset in Aria on cycle 1 only), can be added manually cycle 2 onwards if needed

- Anti-emetics

As take home medication
- metoclopramide 10mg three times a day when required oral
- ondansetron 8mg once a day on days 1, 2, 3, 4 and 5 oral

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

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

- Gastric protection with a H2 antagonist or a proton pump inhibitor due to cyclophosphamide.

- Mouthwashes according to local or national policy on the treatment of mucositis.

Coding

- Procurement – X71.3

- Delivery – X72.2

References

1. Dimopoulos MA, Anagnostopoulos A, Kyrtsonis MC, et al. Primary treatment of Waldenström macroglobulinemia with dexamethasone, rituximab, and cyclophosphamide. J Clin Oncol. 2007 Aug 1;25(22):3344-9.
2. Dimopoulos MA, Kastritis E, Owen RG et al. Treatment recommendations for patients with Waldenström macroglobulinemia (WM) and relaed disorders: IWWM-7 consensus. Blood. 2014 Aug 28;124(9):1404-11
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)
5. Thames Valley Strategic Clinical Network Lymphoma Group Protocol DRC (Dexamethasone + Rituximab + Cyclophosphamide) Published May 2015, Reviewed May 2018, Review due May 2020.

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REGIMEN SUMMARY

Lymphoma – DRC – Cyclophosphamide – Dexamethasone - Rituximab

Cycle 1 Day 1

1. Chlorphenamine 10mg intravenous injection

2. Dexamethasone 20mg intravenous equivalent
   Administration Instructions
   Administer 20mg intravenous equivalent

3. Paracetamol 1000mg oral

4. Rituximab 100mg intravenous infusion in 50ml sodium chloride 0.9% over 120minutes
   Omit rituximab if total IgM is more than 40g/l
   Split dose of rituximab if total IgM more than 20g/l
   If IgM less than 20 give total 375mg/m^2 in 500ml sodium chloride 0.9% on day 1(omit day 2 rituximab dose). Administer according to rituximab 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 related bronchospasm

Cycle 1 Day 2

7. Chlorphenamine 10mg intravenous injection

8. Hydrocortisone 100mg intravenous
   Administration Instructions
   Dexamethasone is part of chemotherapy and is given as part of premedication on day 1

9. Paracetamol 1000mg oral

10. Rituximab 325mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

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

12. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines

13. Cyclophosphamide 100mg/m^2 twice a day for 5 days oral
    Administration Instructions

Oral chemotherapy. Only available as 50mg tablets, please ensure dose modifications occur in multiples of 50mg
Swallow whole, not to be chewed, take with plenty of water
If rituximab is omitted ensure dexamethasone 20mg oral day 1 is prescribed – this is part of chemotherapy regimen (not just premedication for rituximab)

14. Metoclopramide 10mg three times a day when required oral

15. Ondansetron 8mg twice a day for 5 days oral starting before the first dose of cyclophosphamide.

16. Allopurinol 300mg once a day oral
    Administration Instructions
    Take in the morning with food and plenty of water. Continue until bulk of disease is reduced.

17. Aciclovir 400mg twice a day for 21 days oral
    Administration Instructions
    Please supply 21 days or an original pack if appropriate.

18. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;
    - ranitidine 150mg twice a day oral
    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral

    Please supply 21 days or the nearest original pack size.

Cycles 2 onwards

19. Chlorphenamine 10mg intravenous injection

20. Dexamethasone 20mg intravenous equivalent
    Administration Instructions
    Administer 20mg intravenous equivalent

21. Paracetamol 1000mg oral

22. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
    Omit rituximab if total IgM level is more than 40g/l and start as split dose if IgM is more than 20g/l (see cycle 1 for split dosing method)

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

24. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take Home Medicines

25. Cyclophosphamide 100mg/m^2 twice a day for 5 days oral
    Administration Instructions
    Oral chemotherapy. Only available as 50mg tablets, please ensure dose modifications occur in multiples of 50mg.
    Swallow whole, not to be chewed, take with plenty of water
    If rituximab is omitted ensure dexamethasone 20mg oral day 1 is prescribed – this is part of chemotherapy regimen (not just premedication for rituximab)

26. Metoclopramide 10mg three times a day when required oral

27. Ondansetron 8mg twice a day for 5 days oral starting before the first dose of cyclophosphamide.

28. Aciclovir 400mg twice a day for 21 days oral
    Administration Instructions
    Please supply 21 days or an original pack if appropriate.

29. Gastric Protection
    Administration Instructions
    The choice of gastric protection is dependent on local formulary choice and may include;
    - ranitidine 150mg twice a day oral
    - esomeprazole 20mg once a day oral
    - omeprazole 20mg once a day oral
    - lansoprazole 15mg once a day oral
    - pantoprazole 20mg once a day oral
    - rabeprazole 20mg once a day oral
    - cimetidine 400mg twice a day oral
    - famotidine 20mg once a day oral
    - nizatidine 150mg twice a day oral

    Please supply 21 days or the nearest original pack size.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.0	Sept 2019		Harriet Launders Pharmacist	Dr Andrew Duncombe 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 Hospitals 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 which occur as a result of following these guidelines.