Chemotherapy Protocol

LYMPHOMA

RITUXIMAB-GEMCITABINE-OXALIPLATIN (R-GemOx)

Regimen

- Lymphoma – Rituximab-Gemcitabine-Oxaliplatin (R-GemOx)

Indication

- Salvage regimen for relapsed/refractory lymphoma

Toxicity

Drug	Adverse Effect
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy
Gemcitabine	Peripheral oedema, diarrhoea, constipation, rash, respiratory problems, influenza-like symptoms, radiosensitising
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)

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 including magnesium and calcium.

- Check hepatitis B status before starting treatment with rituximab

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

Neutrophils ($x10^9/L$)		Platelets ($x10^9/L$)	
<1.0	OR	<100	Delay until count recovery.

Hepatic Impairment

Drug	Bilirubin µmol/L		AST/ALT units/L	Dose (% of original dose)
Rituximab	N/A		N/A	No dose adjustment needed
Oxaliplatin				Limited information available but there is probably little need to adjust the dose.
Gemcitabine	Greater than 27		n/a	Initiate dose at 800mg/m^2

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Rituximab	N/A	No dose adjustment needed
Oxaliplatin		For moderate renal impairment treat at normal dose and monitor renal function. Dose adjust according to toxicity. If the CrCl is less than 30ml/min then dose reduce.
Gemcitabine	<30ml/min	Consider dose reduction

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.

Gemcitabine may be reduced to 750mg/m^2 to maintain dose intensity

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

Oxaliplatin

If the neurosensory toxicity is NCI-CTC grade 1–2 and lasts less than 7 days administer full dose oxaliplatin. If the toxicity is NCI-CTC grade 2 and persists for more than 7 days reduce the oxaliplatin dose to 75mg/m2 . Oxaliplatin should be discontinued for neurosensory toxicities NCI-CTC grade 3 or above.

If NCI-CTC grade 3-4 diarrhoea or stomatitis recurs despite appropriate reduction in the dose the oxaliplatin dose should be reduced to 75mg/m2 . There are rare case reports of acute interstitial lung disease or lung fibrosis in association with oxaliplatin. Where an unexplained respiratory symptom occurs stop treatment until pulmonary investigations have been conducted to exclude an interstitial cause.

Regimen

2 week cycle (6 cycles set in aria)

Drug	Dose	Days	Administration
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%
Gemcitabine	1000mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
Oxaliplatin	100mg/m^2	1	Intravenous infusion in 500ml

			glucose 5% in 120 minutes

Dose Information

- Rituximab dose will be rounded to the nearest 100mg (up if halfway)
- Gemcitabine will be dose banded in accordance with the national dose bands (38mg/ml)
- Oxaliplatin will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

Extravasation

- Rituximab – neutral
- Gemcitabine – neutral
- Oxaliplatin - exfoliant

Other

- 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

  As take home medication
  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day for 3 days oral
  -dexamethasone 4mg twice a day for 3 days oral

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

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

- 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.

- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral
  - dexamethasone 8mg oral or intravenous

- 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 for 7 days for the first cycle where appropriate

- Growth factor according to local formulary choice.
  For example;
  - filgrastim or bioequivalent 300microgram once a day subcutaneous for seven days starting on day five of the cycle
  - lenograstim or bioequivalent 263microgram once a day subcutaneous for seven days starting on day five of the cycle
  - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two of the cycle

References

1. Celltrion Healthcare UK Limited. Truxima 500mg concentrate for solution for infusion summary of product characteristics. Available from: www.medicines.org.uk/emc/product/9701/smpc. Last updated 22/12/2021 (accessed 23/09/2022).
2. Accord healthcare limited. Gemcitabine 1g powder for solution for infusion summary of product characteristics. Available from: www.medicines.org.uk/emc/product/2490/smpc. Last updated 28/02/2019 (accessed 23/09/2022).
3. Oxaliplatin 5mg/ml concentrate for solution for infusion summary of product characteristics. Available from: www.medicines.org.uk/emc/product.3024/smpc. Last updated 18/05/2022 (accessed 23/09/2022).
4. Mounier N, Gnaoui TW, Tilly H et al. Rituximab plus gemcitabine and oxaliplatin in patients with refractory/relapsed diffuse large b-cell lymphoma who are not candidates for high-dose therapy. A phase II lymphoma study association trial. Haematological. 2013; 98 (11): 1726-31.

REGIMEN SUMMARY

Rituximab-Gemcitabine-Oxaliplatin (R-GemOX)

Cycle 1 Day One

1. Dexamethasone 8mg Oral
   Administration instructions:
   Administer 30 minutes prior to Rituximab. This may be given as dexamethasone 8mg IV stat if required.

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

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

4. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
   Administration instructions
   The rate of administration varies. Please refer to the rituximab administration guidelines.

5. Ondansetron 8mg Oral
   Administration instructions
   Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat if required.

6. Gemcitabine 1000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

7. Oxaliplatin 100mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes
   Administration instructions:
   The rate of administration may be increased to 360 minutes if the patient suffers from an acute larynogopharyngeal dysphagia.

8. Hydrocortisone 100mg intravenous once only when required for the relief of rituximab infusion related reactions
   Administration instruction
   When required for the relief of infusion related reactions

9. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm
   Administration instruction
   When required for the relief of infusion related reactions

Take home medicines

10. Dexamethasone 4mg tablet twice a day for 3 days, oral
    Administration Instructions:
    Take with or after food starting the day after chemotherapy

11. Metoclopramide 10mg tablet three times a day when required, oral
    Administration instructions
    When required for the relief of nausea. Please supply 5 days or an original pack if appropriate.

12. Ondansetron 8mg tablet twice a day for 3 days. Oral
    Administration Instructions

Starting the evening of day 1 of treatment

13. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice

14. Growth factor injection take as directed
    Administration Instructions
    - Filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 5 of the cycle subcutaneous
    - Lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 5 of the cycle subcutaneous
    - Pegfilgrastim or bioequivalent 6mg stat on the day after chemotherapy, subcutaneous.

15. Allopurinol 300mg tablet once a day for 7 days, oral
    Administration Instructions
    Take with or after food with plenty of water. Supply 7 tablets or an original pack as appropriate.

Cycle 2 Day One onwards

16. Dexamethasone 8mg Oral
    Administration instructions:
    Administer 30 minutes prior to rituximab. This may be given as dexamethasone 8mg IV stat if required.

17. Chlorphenamine 10mg intravenous injection
    Administration instructions:
    Administer 30 minutes prior to rituximab

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

19. Rituximab 375mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
    Administration instructions
    The rate of administration varies. Please refer to the rituximab administration guidelines.

20. Ondansetron 8mg Oral
    Administration instructions
    Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat if required.

21. Gemcitabine 1000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

22. Oxaliplatin 100mg/m^2 intravenous infusion in 500ml glucose 5% over 120 minutes
    Administration instructions:
    The rate of administration may be increased to 360 minutes if the patient suffers from an acute larynogopharyngeal dysphagia.

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

24. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm
    Administration instruction
    When required for the relief of infusion related reactions

Take home medicines

25. Dexamethasone 4mg tablet twice a day for 3 days, oral
    Administration Instructions:
    Take with or after food starting the day after chemotherapy

26. Metoclopramide 10mg tablet three times a day when required, oral
    Administration instructions
    When required for the relief of nausea. Please supply 5 days or an original pack if appropriate.

27. Ondansetron 8mg tablet twice a day for 3 days. Oral
    Administration Instructions
    Starting the evening of day 1 of treatment

28. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 28 days oral
    Administration Instructions Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 28 days. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice

29. Growth factor injection take as directed
    Administration Instructions
    - Filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 5 of the cycle subcutaneous
    - Lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 5 of the cycle subcutaneous
    - Pegfilgrastim or bioequivalent 6mg stat on the day after chemotherapy, subcutaneous.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	September 2022	None	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 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.