Chemotherapy Protocol

LYMPHOMA

RITUXIMAB-DEXAMETHASONE-CYTARABINE-OXALIPLATIN (R-DHAOx)

Regimen

- Lymphoma – Rituximab-Dexamethasone-Cytarabine-Oxaliplatin (R-DHAOx)

Indication

- Front line treatment of mantle cell lymphoma (4 cycle therapy)
- Relapsed or refractory Hodgkin and non-Hodgkin lymphoma (3 cycle therapy)

Toxicity

Drug	Adverse Effect
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy
Dexamethasone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Oxaliplatin	Peripheral neuropathy (cumulative), acute laryngopharyngeal dysasthesia (increase duration of infusion)
Cytarabine	Nausea, vomiting, diarrhoea, fever, rash, itching, anorexia, oral and anal inflammation or ulceration, hepatic dysfunction, ocular pain, foreign body sensation, photophobia and blurred vision, dizziness, headache, confusion, cerebellar toxicity, myalgia and bone pain

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

Patients with HODGKIN'S lymphoma carry a lifelong risk of transfusion associated graft versus host disease. Where blood products are required, these patients must receive only irradiated blood products for life. Local blood transfusion departments must be notified as soon as the decision to treat is made and the patient must be issued with an alert card to carry with them at all times.

Monitoring

Re-assessment

- Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
- Record stage of disease - PET-CT / CT scan with contrast (chest, abdomen and pelvis), presence or absence of B-symptoms, clinical extent of disease, consider bone marrow trephine.
- Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, HbA1c, Igs, β2 microglobulin, at baseline and prior to day 1 of each cycle as clinically required
- Baseline hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV, HTLV-1, glucose 6-phosphate dehydrogenase (G6PD) when indicated; group and save.
- Assess glycaemic control as steroids in this regimen can increase the risk of hyperglycaemia. All patients should have a baseline HbA1c and venous plasma glucose checked prior to commencing treatment, followed by venous plasma glucose checked at each cycle and antidiabetic medications managed according to local policies
- Irradiated blood products if used for Hodgkin lymphoma and/or for priming for stem cell collection.
- Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of childbearing age unless they are post-menopausal, have been sterilised or had a hysterectomy.
- ECG +/- ECHO - if clinically indicated.
- Record performance status [ECOG].
- Record vital signs, height and weight.
- Consent and counselling - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
- Fertility - it is very important the patient understands the potential risk of infertility. All patients should be offered fertility advice.
- Assess and document tumour lysis risk as part of pre-assessment. Hydration – in patients with bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours.
- This regimen can be delivered during an inpatient stay or can be used in ambulatory setting for patient(s) meeting the criteria. Refer to local Ambulatory Care Operational Policy.
- Treatment should be agreed in the relevant MDT.

When R-DHAOx regimen is used for priming and harvesting:

- Re-stage after 3 cycles with PET CT and marrow. Collect post cycle 4.
- Stem cell collection should be performed on days 14-16 of the cycle. Ensure that the priming cycle of R-DHAOx starts on a Monday or Tuesday, with G-CSF 1MU/kg starting the following Monday (day 7 or 8).
- Aim to collect 4.0x106 CD34-positive cells/kg [minimum of 2.0x106 CD34-positive cells/kg].

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	**Hepatic impairment**	**Dose (% of original dose)**
Rituximab	N/A	No dose adjustment needed
Oxaliplatin	N/A	Limited information available but there is probably little need to adjust the dose.
Cytarabine	Mild and moderate hepatic impairment	No dose adjustment needed, clinical decision
	Severe hepatic impairment	consider 25-50% of the original dose and increase if tolerated

Renal Impairment

Drug	**Creatinine Clearance (ml/min)**	**Dose (% of original dose)**
Rituximab	N/A	No dose adjustment needed

Oxaliplatin	CrCl ≥ 30ml/min	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.
	CrCl <30ml/min	Contraindicated (SmPC), consider 50% dose (off-label)
Cytarabine	CrCl ≥ 60 ml/min	No dose adjustment needed
	CrCl 31-59 ml/min	50% dose
	CrCl < 30 ml/min	Contraindicated

Neurotoxicity

Drug	Neurotoxicity	Dose (% of original dose)
Oxaliplatin	Grade 2	Reduce dose to 100 mg/m2
	Grade 3 or above or unresolved Grade 2	Omit until symptoms improve then restart at 75 mg/m2

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

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.

Cytarabine

Cytarabine may cause conjunctivitis. The prophylactic use of corticosteroid eye drops may reduce the incidence of this ocular toxicity.

Regimen

3 week cycle (4 cycles set in aria)

Day(s)	Drug	Dose	Route	Administration
1-4	Dexamethasone	40mg	PO	Day 1, if rituximab given: at least 30 minutes prior to rituximab infusion. Take with or just after food in the morning.
1	Rituximab	375mg/m^2	IV	Intravenous infusion in 500ml sodium chloride 0.9%
1	Oxaliplatin	130mg/m^2	IV	Intravenous infusion in 500ml glucose 5% in 120 minutes
2	Cytarabine	2000 mg/m2 every 12 hours	IV	**Administer via CADD Solis VIP pump.** Each infusion bag contains **TWO doses** (500ml total volume). connect infusion bag on Day 1 (first dose AM day 2) and disconnect on day 3 (after day 2 PM dose) **Each dose**: IV infusion of 2000mg/m^2 in 250ml sodium chloride 0.9% over 120 minutes.
2	**Sodium Chloride 0.9%** **(delivered via folfusor pump)**	100ml (at 0.5ml/h)	IV	Sodium chloride 0.9% to be administered via folfusor pump at 0.5ml/hr. To be connected via Y-site with CADD pump to maintain line patency. Disconnect folfusor at the same time as disconnecting CADD infusion bag

Dose Information

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

- Oxaliplatin will be dose banded in accordance with the national dose bands (5mg/ml)

Administration Information

CADD pump

- A total of 2 doses will be provided in one infusion cassette, to be administered as intermittent infusion via a CADD pump for 8AM and 8PM dose.

- Sodium chloride 0.9% 100ml to be run as continuous infusion to keep CADD infusion line patent. Administer concurrently with cytarabine via Y-site with at 0.5 mL/hour on day 2. This infusion device should be connected and disconnected at the same time of cytarabine CADD Cassette

Extravasation

- Rituximab – neutral

- Cytarabine – neutral (irritant in large volumes)

- Oxaliplatin - exfoliant

Other

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

- The daily doses of cytarabine should be given 12 hours apart.

Additional Therapy

This regimen can be administered as inpatient or in the ambulatory setting.
Please ensure all supportive and take-home medicines are prescribed on the inpatient chart (if inpatient) or general electronic prescribing system (if ambulatory setting).

- Rituximab premedication (30 minutes prior to rituximab)
  - chlorphenamine 10mg intravenous bolus
  - 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 corticosteroids.

- TLS prophylaxis
  - Allopurinol 300mg oral once a day for first 7 days (cycle 1 only). Consider rasburicase 3mg OD if high risk TLS.

- Antiemetics
  - ondansetron 8mg TWICE a day on days 1-2, oral or intravenous
  - metoclopramide 10mg three times a day on days 1-5, and when required afterwards, oral or intravenous

- Anti-infective prophylaxis
  - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday (during treatment and at least 3 months after completion)
  - Aciclovir 400mg twice a day oral (during treatment and for 3 months after completion)
  - Fluconazole 50mg OD for the duration of treatment

- Gastric protection with a proton pump inhibitor or a H2 antagonist

- Prednisolone eye drops 0.5% into each eye four times a day from day 2 and continue for 5 days after last cytarabine dose

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

- Supportive antimicrobials may be supplied with direction to only commence if and when directed by the haematology team.
  - Posaconazole 300mg once daily oral
  - Ciprofloxacin 250mg twice daily oral

References

1. Tessoulin B et al. Oxaliplatin before autologous transplantation in combination with high-dose cytarabine and rituximab provides longer disease control than cisplatin or carboplatin in patients with mantle-cell lymphoma: results from the LyMA prospective trial. Bone Marrow Transpl 2021 (online).
2. Lacout et al. R-DHA-oxaliplatin (RDHAOx) versus R-DHA-cisplating (R-DHAP regimen in B-cell lymphoma treatment: An eight year trajectory study. Eur J Haematol 2020. 105:223-230.
3. Le Gouill S et al. Rituximab after Autologous Stem -Cell Transplantation in Mantle-Cell Lymphoma. New Eng J Med 2017. 377:1250-1260.
4. 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.
5. Hospira UK Ltd. Oxaliplatin Hospira 5 mg/ml concentrate for solution for infusion. Summary of Product Characteristics (SmPC). Last updated 13/04/2021. Available at https://www.medicines.org.uk/emc/
6. Aspen. Dexamethasone Tablets BP 2.0mg. Summary of Product Characteristics (SmPC). Last updated 14/08/2022. Available at https://www.medicines.org.uk/emc/.
7. Hospira UK Ltd. Cytarabine 20 mg/ml Solution for Injection/Infusion. Summary of Product Characteristics (SmPC). Last updated 04/04/2024. Available at https://www.medicines.org.uk/emc/.

REGIMEN SUMMARY

Rituximab-Dexamethasone-Cytarabine-Oxaliplatin (R-DHAOx)

Day One

1. Warning – Check blood transfusion status
   Administration Instructions
   Patients with HODGKIN'S lymphoma carry a lifelong risk of transfusion associated graft versus host disease. Where blood products are required, these patients must receive ONLY IRRADIATED BLOOD PRODUCTS for life. Ensure transfusion departments are notified, and the patient has been issued with an alert card to carry with them at all times.

2. Warning – Check supportive medication prescribed (if inpatient)
   Administration instructions: If an in-patient, ensure the following medicines are prescribed on the inpatient chart
   1. Dexamethasone 40mg once a day, days 1 to 4 oral or intravenous
   2. Ondansetron 8mg twice a day, days 1 to 2 oral or intravenous.
   3. Metoclopramide 10mg three times a day, days 1 to 5, then three times a day as required afterward, oral or intravenous
   4. Aciclovir 400mg oral twice a day
   5. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday
   6. Fluconazole 50mg once a day
   7. Growth factors according to local formulary choice. For example:
      - filgrastim or bioequivalent 300microgram once a day subcutaneous for seven days starting on day nine of the cycle
      - lenograstim or bioequivalent 263microgram once a day subcutaneous for seven days starting on day nine of the cycle
      - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day three of the cycle
   8. Thromboprophylaxis with a low molecular weight heparin until platelets are less than $50x10^9$ /L
   9. Gastric protection
   10. Prednisolone 0.5% minims eye drops. 1 drop into both eyes four times a day on days 2-7
   10. Tumour lysis prophylaxis including appropriate hydration (cycle one only)
   15. Consider mouthwashes
   16. Consider norethisterone for menstruating women.

3. Dexamethasone 40mg Oral
   Administration instructions:
   Administer 30 minutes prior to Rituximab. This may be given as dexamethasone 40mg IV stat if required.

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

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

6. 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.

7. Ondansetron 8mg Oral or intravenous
   Administration instructions
   Administer 15-30 minutes prior to chemotherapy.

8. Metoclopramide 10mg Oral or intravenous
   Administration instructions
   Administer 15-30 minutes prior to chemotherapy

9. Oxaliplatin 130mg/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.

10. 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

11. 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 (ambulatory care setting only)

12. Dexamethasone 40mg tablet ONCE a day for 3 days, oral
    Administration Instructions:
    Take in the morning, with or after food starting on day 2

13. Metoclopramide oral 10mg three times a day for 5 days, starting in the afternoon of day 1. From day 6 onwards, take 10mg three times a day when required
    Administration instructions –Please supply 28 tablets or an original pack as appropriate.

14. Ondansetron 8mg tablet twice a day for 2 days
    Administration Instructions
    Starting the evening of day 1 of treatment

15. Allopurinol 300mg tablet once a day for 7 days, oral (Cycle 1 only)
    Administration Instructions
    Take with or after food with plenty of water. Supply 7 tablets or an original pack as appropriate.

16. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday only for 21 days oral
    Administration Instructions Co-trimoxazole 960mg once a day on Mondays, Wednesdays and Fridays. Please supply 21 days. This may be dispensed as 480mg twice a day on Mondays, Wednesdays and Fridays according to local practice

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

18. Fluconazole 50mg oral once a day
    Administration Instructions Please supply 21 days or an original pack if appropriate

19. Prednisolone 0.5% minims eye drops. Starting on day 2, Instil 1 drop into both eyes four times a day for 6 days

20. Gastric Protection
    Administration Instructions: The choice of gastric protection is dependent on local formulary choice and may include;
    - 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
    - ranitidine 150mg twice a day oral

    Please supply 21 days or an original pack if appropriate

21. Growth factor injection take as directed
    Administration Instructions
    - Filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 9 of the cycle subcutaneous
    - Lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 9 of the cycle subcutaneous
    - Pegfilgrastim or bioequivalent 6mg stat on day 3, subcutaneous.

Day TWO

22. Warning – check pre-medication

Administration instructions:
Confirm patient has taken the following premeds in the morning of day 2:
- Dexamethasone 40mg tablets oral
- Ondansetron 8mg tablets oral
- Metoclopramide 10mg tablets oral

23. Warning – Cytarabine delivered via one CADD

Administration Instructions
Cytarabine is administered TWICE a day at 12 hour intervals (**0800 and 2000**) via CADD pump. Sodium chloride infusion must be administered concurrently.
Always refer to the patient schedule for supportive treatments and fluids

24. Cytarabine 4000mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as intermittent infusions via CADD pump

Administration Instructions
The daily doses of cytarabine should be given 12 hours apart
One dose: Cytarabine 2000mg/m^2 in 250ml sodium chloride 0.9% over 120 minutes.
Each infusion bag contains: 2 doses
Cytarabine is administered TWICE a day at 12-hour intervals (0800 and 2000) on day 2 (2 doses in total).
Connect infusion bag on day 1 and disconnect on day 3 (if on ambulatory setting)

25. Sodium Chloride 0.9% 100ml continuous infusion at 0.5ml/hr.

Administration Instructions
Sodium chloride 0.9% to be administered via folfusor pump at 0.5ml/hr on Day 2.
To be connected via Y-site with CADD pump to maintain line patency.
Disconnect folfusor at the same time as disconnecting CADD cassette

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	August 2026	New regimen	Alexandre Guedes Pharmacist	Robert 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.