Chemotherapy Protocol

LYMPHOMA

CISPLATIN-DEXAMETHASONE-GEMCITABINE-RITUXIMAB

(RGDP)

Regimen

- Lymphoma – RGDP-Cisplatin-Dexamethasone-Gemcitabine-Rituximab

Indication

- Patients with relapsed aggressive B-cell non-Hodgkin's lymphomas with good performance status who are being treated with curative intent

Toxicity

Drug	Adverse Effect
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Dexamethasone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Gemcitabine	Peripheral oedema, diarrhoea, constipation, rash, respiratory problems, influenza-like symptoms, radiosensitising
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 and U&Es prior to day one and eight of treatment
- LFTs prior to day one of treatment
- EDTA or calculated creatinine clearance before day one
- Regular monitoring of blood glucose
- Consider formal audiology testing
- Check hepatitis B status before starting 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

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.

Day 1

Neutrophils ($x10^9$/L)		**Platelets ($x10^9$/L)**	**Dose Modifications (cisplatin and gemcitabine)**
greater than or equal to 1	AND	greater than or equal to 75	100%
greater than or equal to 1	AND	less than 75	Delay 1 week, if platelets are greater than or equal to 50 then give 100% with platelet transfusions as necessary.
less than 1	AND	greater than or equal to 75	Delay 1 week, if neutrophils are greater than or equal to 0.5 then give 100% with G-CSF support
less than 1	AND	less than 75	Delay 1 week: If neutrophils are greater than or equal to 0.5 AND platelets are greater than or equal to 50 then give 100% with G-CSF and platelet transfusions as necessary. If neutrophils are less than 0.5 AND/OR platelets are less than 50 hold treatment, re-check blood counts every 3 days, resume treatment once neutrophils and platelets are greater or equal to 0.5 and 50 respectively

Day 8

Neutrophils ($x10^9$/L)		Platelets ($x10^9$/L)	Dose Modifications (gemcitabine)
greater than or equal to 1	AND	greater than or equal to 75	100%
0.5 - 0.9	AND	greater than or equal to 75	Give 100% and support with G-CSF OR Give 75% of original dose
greater than or equal to 0.5	AND	50-75	Give 75% of original dose
less than 0.5	OR	less than 50	Omit

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)
Cisplatin	N/A		N/A	No dose adjustment needed
Gemcitabine	greater than 30*		N/A	Initiate treatment with a dose of 800mg/m^2
Rituximab	N/A		N/A	No dose adjustment needed

* Limit reflects local practice and may vary from published sources

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cisplatin	more than 60	100%
	40-59	75%
	less than 40	Consider alternative
Gemcitabine	greater than or equal to 30	100%
	less than 30	Consider dose reduction
Rituximab	N/A	No dose adjustment needed

Cisplatin

Ototoxicity of grade 2 or above, discuss with consultant – dose may need to be reduced.

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 clinically significant grade 3 non-haematological toxicities reduce gemcitabine and cisplatin doses to 75%.
For all other clinically significant grade 4 non-haematological toxicities reduce gemcitabine and cisplatin doses to 50%.

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 3-6 cycles (3 cycles will be set in ARIA)

Drug	Dose	Days	Administration
Dexamethasone	40mg	1,2,3,4	Oral
Cisplatin	75mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over 120 minutes (max rate is 1mg cisplatin/minute)
Gemcitabine	1000mg/m^2	1, 8	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9%
G-CSF	1 dose	9-15	Subcutaneous

Dose Information

- Cisplatin will be dose banded in accordance with the national dose bands (1mg/ml)
- Gemcitabine will be dose banded in accordance with the national dose bands (100mg/ml)
- Rituximab will be dose rounded to the nearest 100mg (up if half way)

Administration Information

Extravasation

- Cisplatin – exfoliant
- Gemcitabine – neutral
- Rituximab - neutral

Other

- Dexamethasone tablets to be taken in the morning with or after food
- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy on **day 1**

  - aprepitant 125mg oral
  - ondansetron 8mg oral or intravenous

  As take home medication on day 1

  - aprepitant 80mg once a day for 2 days starting on day two of treatment
  - metoclopramide 10mg three times a day oral as necessary
  - ondansetron 8mg twice a day for 3 days starting on the evening of day one of treatment

  15-30 minutes prior to chemotherapy on **day 8**

  - metoclopramide 10mg oral or intravenous

- Cisplatin pre and post hydration as follows

  Pre

  Furosemide 40mg oral or intravenous

  1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol

magnesium sulphate over 60 minutes

Post

1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.

- Rituximab pre-medication

  30 minutes prior to rituximab
  - dexamethasone (this is part of the chemotherapy schedule as well as the premedication)
  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral

- 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 for 7 days oral for the first cycle only

- Anti-infective prophylaxis including:

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

- Growth factor on days 9 to 15. For example:
  - filgrastim or bioequivalent 30 million units once a day for 7 days from day 9 subcutaneous
  - lenograstim or bioequivalent 33.6 million units once a day for 7 days from day 9 subcutaneous

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

- Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Coding

- Procurement – X70.8

- Delivery – X72.9 Day 1, X72.4 Day 8

References

1. Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014 Nov 1;32(31):3490-6

REGIMEN SUMMARY

RGDP-Cisplatin-Dexamethasone-Gemcitabine-Rituximab

Cycle 1 Day 1

1. Dexamethasone 40mg oral
2. Chlorphenamine 10mg 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. Aprepitant 125mg oral
6. Ondansetron 8mg oral or intravenous
7. Gemcitabine 1000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
8. Furosemide 40mg oral or intravenous
9. Sodium chloride 0.9% 1000ml with 20mmol potassium chloride and 16mmol magnesium sulphate intravenous infusion over 60 minutes
10. Cisplatin 75mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes (maximum rate 1mg cisplatin/minute)
11. Sodium chloride 0.9% 1000ml with 20mmol potassium chloride and 16mmol magnesium sulphate intravenous infusion over 60 minutes
12. Hydrocortisone 100mg intravenous bolus once only when required for the relief of rituximab infusion related reactions
13. Salbutamol 2.5mg nebule once only when required for the relief of rituximab related bronchospasm

Take home medicines (day 1 only)

14. Dexamethasone 40mg once a day oral for 3 days starting on day two of treatment
15. Aprepitant 80mg once a day oral for 2 days starting on day two of treatment
16. Metoclopramide 10mg three times a day oral as necessary
17. Ondansetron 8mg twice a day oral for 3 days starting on the evening of day one of treatment
18. Aciclovir 400mg twice a day oral for 21 days

19. Co-trimoxazole 960mg once a day oral on Mondays, Wednesdays and Fridays for 21 days

20. Growth Factor
    Administration Instructions
    Growth factor as per local formulary choice:
    - 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

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

Cycle 1 Day 8

22. Metoclopramide 10mg oral or intravenous

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

Cycle 2 & 3 Day 1

24. Dexamethasone 40mg oral

25. Chlorphenamine 10mg intravenous

26. Paracetamol 1000mg oral

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

28. Aprepitant 125mg oral

29. Ondansetron 8mg oral or intravenous

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

31. Furosemide 40mg oral or intravenous

32. Sodium chloride 0.9% 1000ml with 20mmol potassium chloride and 16mmol magnesium sulphate intravenous infusion over 60 minutes

33. Cisplatin 75mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride intravenous infusion over 120 minutes (maximum rate 1mg cisplatin/minute)

34. Sodium chloride 0.9% 1000ml with 20mmol potassium chloride and 16mmol magnesium sulphate intravenous infusion over 60 minutes

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

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

Take home medicines (day 1 only)

37. Dexamethasone 40mg once a day oral for 3 days starting on day two of treatment

38. Aprepitant 80mg once a day oral for 2 days starting on day two of treatment

39. Metoclopramide 10mg three times a day oral as necessary

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

41. Aciclovir 400mg twice a day oral for 21 days

42. Co-trimoxazole 960mg once a day oral on Mondays, Wednesdays and Fridays for 21 days

43. Growth Factor
    Administration Instructions
    Growth factor as per local formulary choice:
    - 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

Cycle 2 & 3 Day 8

44. Metoclopramide 10mg oral or intravenous

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	June 2019	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Robert 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 which occur as a result of following these guidelines.