Chemotherapy Protocol

LYMPHOMA

CYCLOPHOSPHAMIDE-GEMCITABINE-PREDNISOLONE-RITUXIMAB-VINCRISTINE

(RGCVP)

Regimen

- Lymphoma–RGCVP-Cyclophosphamide-Gemcitabine-Prednisolone-Rituximab-Vincristine

Indication

- CD20 positive Non-Hodgkin's Lymphoma in the elderly and patients considered unsuitable for anthracycline-based chemotherapy.

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Gemcitabine	Peripheral oedema, diarrhoea, constipation, rash, respiratory problems, influenza-like symptoms, radiosensitising
Prednisolone	Weight gain, GI disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Rituxumab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy
Vincristine	Peripheral neuropathy, constipation, jaw pain

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 prior to 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

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

Dose modifications based on haematological parameters apply to cyclophosphamide, gemcitabine and vincristine only.

Neutrophils (x10^9/L)	**Dose Modifications (cyclophosphamide, gemcitabine, vincristine)**
1 or greater	100%
0.5 - 0.9	75%
Less than 0.5	Delay until neutrophils are 1x10^9/L or above then continue at full dose
Febrile neutropenia	1st occurrence - delay until recovery then continue at full dose 2nd occurrence – delay until recovery then reduce the dose to 75% of the original for all subsequent cycles
Platelets (x10^9/L)	**Dose Modifications (cyclophosphamide, gemcitabine, vincristine)**
75 or above	100%
50 – 74	75%
Less than 50	Delay until platelets are 75x10^9/L or above then continue at full dose
Thrombocytopenia with haemorrhage	1st occurrence - delay until recovery then continue at full dose 2nd occurrence – delay until recovery then reduce the dose to 75% of the original for all subsequent cycles.

Day 8

Dose modifications based on haematological parameters apply to gemcitabine only.

Neutrophils (x10^9/L)	**Dose Modifications (gemcitabine only)**
1 or greater	100%
0.5 - 0.9	75%
Less than 0.5	omit
Platelets (x10^9/L)	**Dose Modifications (gemcitabine only)**
75 or above	100%
50 – 74	75%
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)**
Cyclophosphamide	Evidence suggests no dose adjustment necessary			
Gemcitabine	more than *30		N/A	Dose escalate with caution
Rituximab	N/A		N/A	No dose adjustment needed
Vincristine	*30-51	or	60-180	50%
	more than 51	and	normal	50%
	more than 51	and	more than180	omit

* Lower limit reflects local practice and may vary from published sources

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide**	more than 20	100%
	10-20	75%
	less than10	50%
Gemcitabine	more than or equal to 30	100%
	less than 30	Consider dose reduction
Rituximab	N/A	No dose adjustment needed
Vincristine	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.

For all other non-haematological NCI-CTC grade 3 toxicities reduce the dose of the causative agent(s) to 75% of the original dose.

For all other non-haematological NCI-CTC grade 4 toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent(s) should then be reduced to 50% 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 prior to treatment may increase the risk of rituximab associated hepatotoxicity. Patients should be assessed for any cold or flu-like symptoms prior to treatment

Vincristine

Reduce the vincristine dose to 1mg if a NCI-CTC grade 2 motor or grade 3 sensory neurological toxicity occurs. For higher toxicity grades or if toxicity increases despite dose reduction stop the vincristine.

Regimen

21 day cycle for 6 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	750mg/m^2	1	Intravenous bolus over 10 minutes
Gemcitabine	750mg/m^2 (cycle 1) 875mg/m^2 (cycle 2) 1000mg/m^2 (cycle 3 onwards)	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%
Vincristine	1.4mg/m^2 (max 2mg)	1	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Prednisolone	100mg	1, 2, 3, 4, 5	Oral

Consider initial dose reduction in patients over 70 years of age. Doses may be escalated up to full dose on subsequent cycles according to tolerability.

Dose Information

- Cyclophosphamide will be dose banded according to the CSCCN agreed bands
- Gemcitabine will be dose banded according to the CSCCN agreed bands
- Rituximab will be dose rounded to the nearest 100mg (up if halfway)
- Vincristine dose will be rounded to the nearest 0.1mg (up if halfway)

- The maximum dose of vincristine is 2mg

Administration Information

Extravasation

- Cyclophosphamide – neutral
- Gemcitabine - neutral
- Rituximab - neutral
- Vincristine - vesicant

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 on day 1

  - 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

  15-30 minutes prior to chemotherapy on day 8

  - metoclopramide 10mg oral or intravenous

- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - paracetamol 1000mg oral

  On the morning of treatment

  - prednisolone 100mg 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 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 the first cycle only

- Growth factors to be started and continued until the neutrophil count is above $1x10^9$/L. For example;

    - filgrastim or bioequivalent 30 million units once a day from day 9 subcutaneous
    - lenograstim or bioequivalent 33.6 million units once a day from day 9 subcutaneous
    - pegfilgrastim or bioequivalent 6mg **once only** day 9 subcutaneous

    A seven day supply will be issued on day 8 of each cycle.

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

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

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

- 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.

Additional Information

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

Coding (OPCS 4.6)

- Procurement – X71.5

- Delivery – X72.1 & X72.4

References

1.A Phase II multicentre trial of Gemcitabine, CVP, and Rituximab (R-GCVP) for the treatment of patients with newly diagnosed Diffuse Large B-Cell Lymphoma, considered unsuitable for R-CHOP Chemotherapy. NCRI Version 6.0 1st April 2009

REGIMEN SUMMARY

RGCVP-Cyclophosphamide-Gemcitabine-Prednisolone-Rituximab-Vincristine

Cycle 1 Day 1

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

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. Ondansetron 8mg oral or intravenous

6. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

7. Gemcitabine 750mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

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

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

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

Take Home Medicines

11. Prednisolone 100mg once a day on the morning of the **next** treatment
    Administration Instructions
    The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

12. Prednisolone 100mg once a day for 4 days oral (starting on day 2)
    Administration Instructions
    The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

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

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

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

Cycle 1 Day 8

16. Metoclopramide 10mg oral or intravenous injection

17. Gemcitabine 750mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Take Home Medicines

18. Growth factor

Administration Instructions

Dispense according to local formulary. For example;

- filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 9 subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 9 subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 9 subcutaneous

Cycle 2 Day 1

1. Warning – Check patient has taken the prednisolone dose

Administration Instructions

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

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. Ondansetron 8mg oral or intravenous

6. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

7. Gemcitabine 875mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Administration Instructions

The dose of gemcitabine for this cycle has been automatically escalated. Please check that the dose is clinically appropriate for this patient.

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

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

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

Take Home Medicines

12. Prednisolone 100mg once a day on the morning of the **next** treatment

Administration Instructions

The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

13. Prednisolone 100mg once a day for 4 days oral (starting on day 2)

Administration Instructions

The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

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

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

Cycle 2 Day 8

16. Metoclopramide 10mg oral or intravenous

17. Gemcitabine 875mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Administration Instructions

The dose of gemcitabine for this cycle has been automatically escalated please check that the dose is clinically appropriate for this patient.

Take Home Medicines

18. Growth factor

Administration Instructions

Dispense according to local formulary. For example;

- filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 9 subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 9 subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 9 subcutaneous

Cycle 3 Day 1

1. Warning – Check patient has taken the prednisolone dose

Administration Instructions

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

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. Ondansetron 8mg oral or intravenous

6. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

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

Administration Instructions

The dose of gemcitabine for this cycle has been automatically escalated. This is the dose for cycles 3, 4, 5, and 6. Please check that the dose is clinically appropriate for this patient.

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

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

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

Take Home Medicines

12. Prednisolone 100mg once a day on the morning of the **next** treatment
    Administration Instructions
    The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

13. Prednisolone 100mg once a day for 4 days oral (starting on day 2)
    Administration Instructions
    The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

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

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

Cycle 3 Day 8

16. Metoclopramide 10mg oral or intravenous

17. Gemcitabine 1000mg/m^2 intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes
    Administration Instructions
    The dose of gemcitabine for this cycle has been automatically escalated. This is the dose for cycles 3, 4, 5, and 6. Please check that the dose is clinically appropriate for this patient.

Take Home Medicines

18. Growth factor
    Administration Instructions
    Dispense according to local formulary. For example;
    - filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 9 subcutaneous
    - lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 9 subcutaneous
    - pegfilgrastim or bioequivalent 6mg once only on day 9 subcutaneous

Cycles 4 and 5 Day 1

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

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. Ondansetron 8mg oral or intravenous

6. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

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

Administration Instructions
The dose of gemcitabine for this cycle has been automatically escalated. This is the dose for cycles 3, 4, 5, and 6. Please check that the dose is clinically appropriate for this patient.

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

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

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

Take Home Medicines

11. Prednisolone 100mg once a day on the morning of the next treatment

Administration Instructions
The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

12. Prednisolone 100mg once a day for 4 days oral (starting on day 2)

Administration Instructions
The prednisolone may be dispensed as a single supply in one container or as two containers depending on local preference

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

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

Cycle 4 and 5 Day 8

15. Metoclopramide 10mg oral or intravenous

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

Administration Instructions
The dose of gemcitabine for this cycle has been automatically escalated. This is the dose for cycles 3, 4, 5, and 6. Please check that the dose is clinically appropriate for this patient.

Take Home Medicines

17. Growth factor

Administration Instructions
Dispense according to local formulary. For example;

- filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 9 subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 9 subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 9 subcutaneous

Cycle 6 Day 1

1. Warning – Check patient has taken prednisolone dose

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

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. Ondansetron 8mg oral or intravenous

6. Vincristine 1.4mg/m^2 (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

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

Administration Instructions
The dose of gemcitabine for this cycle has been automatically escalated. This is the dose for cycles 3, 4, 5, and 6. Please check that the dose is clinically appropriate for this patient.

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

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

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

Take Home Medicines

11. Prednisolone 100mg once a day for 4 days oral (starting on day 2)

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

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

Cycle 6 Day 8

14. Metoclopramide 10mg oral or intravenous injection

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

Administration Instructions
The dose of gemcitabine for this cycle has been automatically escalated. This is the dose for cycles 3, 4, 5, and 6. Please check that the dose is clinically appropriate for this patient.

Take Home Medicines

16. Growth factor

Administration Instructions

Dispense according to local formulary. For example;

- filgrastim or bioequivalent 30 million units once a day for 7 days starting on day 9 subcutaneous
- lenograstim or bioequivalent 33.6 million units once a day for 7 days starting on day 9 subcutaneous
- pegfilgrastim or bioequivalent 6mg once only on day 9 subcutaneous

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Jan 2015	Header changed Toxicities removed Hepatic & renal tables updated Metoclopramide dose changed to 10mg Growth factor units updated Bolus removed from intravenous bolus throughout text Mucositis recommendation changed Ondansetron TTO clarified Disclaimer added	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	Sept 2012	Cycle 2 day 1 on page 11 changed to cycle 3 day 1. Gemcitabine administration instructions cycle 3 to 6 inclusive amended in the summary.	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	July 2012	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Andrew Davies Consultant Medical Oncologist Dr Alison Milne Consultant Haematologist

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.