Chemotherapy Protocol

CHRONIC LYMPHOCYTIC LEUKAEMIA

CYCLOPHOSPHAMIDE-FLUDARABINE-RITUXIMAB (PO-Split)

Regimen

- CLL – RFC (PO)-Cyclophosphamide-Fludarabine-Rituximab (PO-Split)

Indication

- Chronic Lymphocytic Leukaemia
- The rituximab split dose is indicated where the lymphocyte count is greater than $25x10^9/L$

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Fludarabine	Transfusion related GVHD, neurotoxicity, opportunistic infections, GI disturbances
Rituximab	Severe cytokine release syndrome, increased incidence of infective complications, progressive multifocal leukoencephalopathy

Patients treated with fludarabine carry a lifelong risk of transfusion associated graft versus host disease (TA-GVHD). 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.

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

Drugs

- FBC, LFTs and U&Es prior to day one of treatment
- Hepatitis B status prior to starting treatment with rituximab

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and some 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 or erythropoietin if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL. Irradiated blood products must be used (fludarabine).

Dose modifications based on haematological parameters apply to cyclophosphamide and fludarabine only. Rituximab rarely has to be dose adjusted for haematological toxicity.

Neutrophils ($x10^9$/L)	**Dose Modifications (cyclophosphamide and fludarabine)**
more than 1	100%
0.5-1	Delay for 7 days and if counts recover give 100% doses. If 14 days are required for counts to recover then re-start with a 50% dose reduction
Platelets ($x10^9$/L)	**Dose Modifications**
more than 75	100%
50-75	Delay for 7 days and if counts recover give 100% doses. If 14 days are required for counts to recover then re-start with a 50% dose reduction

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	more than 21	or	2-3xULN	Clinical decision. Evidence that exposure to active metabolites may not be increased, suggesting dose reduction may not be necessary
Fludarabine	N/A		N/A	No dose adjustment required
Rituximab	N/A		N/A	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	omit
Fludarabine	greater than 70	100%
	30-70	50%
	less than 30	omit
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.

In general for all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 2 or below. The dose should then be reduced to 75% of the original dose. If toxicity recurs delay until recovery and further dose reduce to 50% of the original dose or discontinue 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 may be 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.

Regimen

28 day cycle for 6 cycles

Cycle 1

Drug	Dose	Days	Administration
Cyclophosphamide	150mg/m^2	2, 3, 4, 5, 6	Oral
Fludarabine	24mg/m^2	2, 3, 4, 5, 6	Oral
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% starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

Cycle 2 onwards

Drug	Dose	Days	Administration
Cyclophosphamide	150mg/m^2	1, 2, 3, 4, 5	Oral
Fludarabine	24mg/m^2	1, 2, 3, 4, 5	Oral
Rituximab	500mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% as per local rituximab administration guidelines*

*If the lymphocyte is greater than 25x10^9/L on day one then consider fractionating the dose of rituximab as follows;

Day 1 - rituximab 125mg/m^2 in 100ml sodium chloride 0.9%
Day 2 - rituximab 375mg/m^2 in 500ml sodium chloride 0.9%

If there were no problems with the previous infusion then start both fractions at 100mg/hour and escalate the rate in 100mg/hour increments every 30 minutes to a maximum rate of 400mg/hour. If reactions occurred with the previous cycle, give both fractions starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

Dose Information

- Cyclophosphamide is available as 50mg tablets. Doses will be rounded to the nearest 50mg (up if halfway)
- Fludarabine is available as 10mg tablets. Doses will be rounded to the nearest 10mg (up if halfway)
- The dose of rituximab from 325mg/m^2 and above will be dose rounded to the nearest 100mg (up if halfway)

Administration Information

Extravasation

- Rituximab - neutral

Other

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

Additional Therapy

- Antiemetics

  As take home medication

  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day on days of chemotherapy administration

- Rituximab pre-medication

  30 minutes prior to rituximab

  - chlorphenamine 10mg intravenous
  - hydrocortisone 100mg 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 bolus for rituximab related rigors that fail to respond to steroids.

- Patients with CLL are at risk of tumour lysis syndrome (TLS). The British Society of Haematology guidelines are a useful reference source. Oral allopurinol is one option for prophylaxis (300mg once a day oral for 7 days in he first cycle will be set in ARIA). Intravenous rasburicase can be considered in high risk individuals.

- Anti-infective prophylaxis with;

  - 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 H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

Coding

- Procurement – X71.5
- Delivery – X72.1, X72.3, X72.4

References
1.Keating M et al. Early Results of a Chemoimmunotherapy Regimen of Fludarabine, Cyclophosphamide, and Rituximab as initial therapy for chronic lymphocytic leukaemia. J Clin Oncol (2005); 23 (18): 4079-4088
2. Tam CS et al. Long-term results of the fludarabine, cyclophosphamide, and rituximab regimen as initial therapy of chronic lymphocytic leukaemia. Blood (2008); 112:975-980
3. Wierda W et al. Chemoimmunotherapy with Fludarabine, Cyclophosphamide, and Rituximab for Relapsed and Refractory Chronic Lymphocytic Leukaemia. J Clin Oncol (2005); 23:4070-4078

REGIMEN SUMMARY

RFC-Cyclophosphamide-Fludarabine-Rituximab (PO-Split)

Cycle 1 Day One

1 Warning – Check blood transfusion status
Administration Instructions
Patients treated with fludarabine 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

2. Chlorphenamine 10mg intravenous

3. Hydrocortisone 100mg intravenous

4. Paracetamol 1000mg oral

5. Rituximab 100mg intravenous infusion in 50ml sodium chloride 0.9% over 120 minutes

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

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

Cycle 1 Day Two

8. Chlorphenamine 10mg intravenous

9. Hydrocortisone 100mg intravenous

10. Paracetamol 1000mg oral

11. Rituximab 325mg/m^2 intravenous infusion in 500ml sodium chloride 0.9%
Administration Guidelines
Start at a rate of 50mg/hour and, if tolerated, increase by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour.

12. Hydrocortisone 100mg intravenous 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 one only)

14. Cyclophosphamide 150mg/m^2 once a day in the morning starting on day 2 of the cycle for 5 days oral
Administration Instructions
Take once a day in the morning starting on day two of the chemotherapy cycle. Oral chemotherapy.

15. Fludarabine 24mg/m^2 once a day at lunchtime starting on day 2 of the cycle for five days oral
    Administration Instructions
    Take once a day at lunchtime starting on day two of the chemotherapy cycle. Oral chemotherapy.

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

17. Metoclopramide 10mg three times a day when required oral
    Administration Instructions
    Supply an original pack of 28 tablets or nearest equivalent

18. Ondansetron 8mg twice a day for 5 days oral starting on the morning of day two of treatment

19. Aciclovir 400mg twice a day for 28 days oral

20. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral

Cycle 2 Day One onwards

21. Chlorphenamine 10mg intravenous

22. Hydrocortisone 100mg intravenous

23. Paracetamol 1000mg oral

24. Rituximab 500mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines
    Administration Instructions
    Administer as per your local administration guidelines

    If the lymphocyte is greater than 25x10^9/L on day one then consider fractionating the dose of rituximab as follows;

    Day 1 - rituximab 125mg/m^2 in 100ml sodium chloride 0.9%
    Day 2 - rituximab 375mg/m^2 in 500ml sodium chloride 0.9%

    If there were no problems with the previous infusion then start both fractions at 100mg/hour and escalate the rate in 100mg/hour increments every 30 minutes to a maximum rate of 400mg/hour. If reactions occurred with the previous cycle, give both fractions starting at a rate of 50mg/hour and, if tolerated, increasing by 50mg/hour every 30 minutes to a maximum rate of 400mg/hour

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

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

Take home medicines (day one only)

27. Cyclophosphamide 150mg/m^2 once a day in the morning starting on day 1 of the cycle for 5 days oral
    Administration Instructions
    Take once a day in the morning starting on day one of the chemotherapy cycle. Oral chemotherapy.

28. Fludarabine 24mg/m^2 once a day at lunchtime starting on day 1 of the cycle for five days oral
    Administration Instructions
    Take once a day at lunchtime starting on day one of the chemotherapy cycle. Oral chemotherapy.

29. Metoclopramide 10mg three times a day when required oral
    Administration Instructions
    Supply an original pack of 28 tablets or nearest equivalent

30. Ondansetron 8mg twice a day for 5 days oral starting on the morning of day one of treatment

31. Aciclovir 400mg twice a day for 28 days oral

32. Co-trimoxazole 960mg once a day on Monday, Wednesday and Friday for 28 days oral

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	March 2017	None	Dr Deborah Wright Pharmacist	Dr Helen Dignum 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 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 that occur as a result of following these guidelines.