Chemotherapy Protocol

Chronic Lymphocytic Leukaemia (CLL)

Chlorambucil (7 day)-Rituximab

Regimen

- CLL – Chlorambucil (7 day)-Rituximab

Indication

- Treatment of CLL in elderly patients for whom treatment with fludarabine and cyclophosphamide or chlorambucil and obinutuzumab or bendamustine is not considered appropriate, due to co-morbidities or performance status
- Disease modification

Toxicity

Drug	Adverse Effect
Chlorambucil	Neutropenia, thrombocytopenia, anaemia, nausea, vomiting, diarrhoea, mouth ulceration, rash
Rituximab	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

- FBC, U&Es and LFTs on day one of the cycle
- 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.

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.

Consider blood transfusion or the use of erythropoietin according to NICE TA323 if the patient is symptomatic of anaemia or where the haemoglobin is less than 8g/dL.

The dose of rituximab is rarely adjusted for haematological parameters.

Neutrophils ($x10^9$/L)		Platelets ($x10^9$/L)	Chlorambucil Dose
more than 1	and / or	more than 75	100%
0.5 - 1	and / or	50 - 75	Delay treatment for one week. If counts recover treatment can be re-started. If the counts take between 8-14 days to recover, treatment may be re-started with a 50% dose reduction
less than 0.5	and / or	less than 50	Delay treatment until the counts have recovered, the restart using a 50% dose reduction

Hepatic Impairment

Patients with hepatic impairment should be closely monitored for signs and symptoms of toxicity.

Since chlorambucil is primarily metabolized in the liver, dose reduction should be considered in patients with severe hepatic impairment. However, there are insufficient data in patients with hepatic impairment to provide a specific dosing recommendation.

Rituximab does not require dose adjustment in hepatic impairment.

Renal Impairment

Dose adjustment is not considered necessary in renal impaired patients.

Patients with evidence of impaired renal function should be carefully monitored as they are prone to additional myelosuppression.

Rituximab does not require dose adjustment in renal impairment.

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 12 cycles

Cycle 1

Drug	Dose	Days	Administration
Chlorambucil	10mg/m^2 once a day	1, 2, 3, 4, 5, 6, 7	Oral
Rituximab	375mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% at a rate of 50mg/hour increasing by 50mg/hour every 30 minutes if tolerated to a maximum rate of 400mg/hour

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Chlorambucil	10mg/m^2 once a day	1, 2, 3, 4, 5, 6, 7	Oral
Rituximab	500mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% as per the rituximab administration guidelines

Cycle 7, 8, 9, 10, 11, 12

Cycle 7 onwards should only be considered for those individual who demonstrate a continuing response to treatment.

Drug	Dose	Days	Administration
Chlorambucil	10mg/m^2 once a day	1, 2, 3, 4, 5, 6, 7	Oral

Dose Information

- Chlorambucil is available as 2mg film-coated tablets.
- The dose of chlorambucil will be rounded to the nearest 2mg (up if halfway)
- The dose of rituximab for the 50mg/m^2 - 125mg/m^2 dose will be rounded as per the national dose bands (10mg/ml)
- The dose of rituximab from 325mg/m^2 and above will be dose rounded to the nearest 100mg (up if halfway)

Administration Information

- Chlorambucil should be swallowed whole on an empty stomach either one hour before meals or three hours after.
- The daily dose may be divided into three (morning, noon and night) if nausea or vomiting is problematic.
- The film-coated tablets should not be crushed or dissolved prior to administration.
- The rate of administration of rituximab varies. Please refer to the rituximab administration guidelines.

Additional Therapy

- No routine anti-emetics are required. They may be added from "favourites" on ARIA for individual patients who may require treatment for nausea and vomiting.
- 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.

- 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.

Additional Information

- The National Patient Safety Alert on oral chemotherapy (NPSA/2008/RRR001) must be followed in relation to chlorambucil.

- It must be made clear to all staff, including those in the community, that chlorambucil is given as a short course that is repeated and should only be prescribed under the supervision of a consultant haematologist.

Coding

- Procurement – X71.3

- Delivery – X72.2

References
1. Foa R, Del Gludice I, Cuneo A et al. Chlorambucil plus rituximab with or without maintenance rituximab as first line treatment for elderly chronic lymphocytic leukemia patients. Am J Hematol 2014; 89 (5): 480-486.
2. Cramer P, Isfort S, Bahlo J et al. Outcome of advanced chronic lymphocytic leukemia following different first line and relapse therapies: a meta-analysis of five prospective trials by the German CLL Study Group. Haematologica 2015; 100 (11): 1451-9.

REGIMEN SUMMARY

Chlorambucil (7 day)-Rituximab

Cycle 1 Day 1

1. Chlorphenamine 10mg intravenous

2. Hydrocortisone 100mg intravenous

3. Paracetamol 1000mg oral

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

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

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

Take Home Medicines (day one only)

7. Chlorambucil 10mg/m^2 once a day for 7 days starting on day 1 of the cycle oral
   Administration Information
   Oral chemotherapy. Start on day 1 of the chemotherapy cycle

   Swallow whole, do not crush or chew. Take on an empty stomach either an hour before food or three hours after.

   The daily dose may be divided into three (morning, noon and night) if adverse effects such as nausea and vomiting occur.

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

Cycles 2, 3, 4, 5, 6

Day 1

9. Chlorphenamine 10mg intravenous

10. Hydrocortisone 100mg intravenous

11. Paracetamol 1000mg oral

12. Rituximab 500mg/m^2 intravenous infusion in 500ml sodium chloride 0.9%
    Administration Instructions
    The rate of administration of rituximab varies. Please refer to your local rituximab administration guidelines.

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

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

Take Home Medicines (day one only)

15. Chlorambucil 10mg/m^2 once a day for 7 days starting on day 1 of the cycle oral
    Administration Information
    Oral chemotherapy. Start on day 1 of the chemotherapy cycle.

    Swallow whole, do not crush or chew. Take on an empty stomach either an hour before food or three hours after.

    The daily dose may be divided into three (morning, noon and night) if adverse effects such as nausea and vomiting occur.

Cycles 7, 8, 9, 10, 11, 12

Take Home Medicines (day one only)

16. Chlorambucil 10mg/m^2 once a day for 7 days starting on day 1 of the cycle oral
    Administration Information
    Oral chemotherapy. Start on day 1 of the chemotherapy cycle

    Swallow whole, do not crush or chew. Take on an empty stomach either an hour before food or three hours after.

    The daily dose may be divided into three (morning, noon and night) if adverse effects such as nausea and vomiting occur.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	February 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.