Chemotherapy Protocol

Chronic Lymphocytic Leukaemia

Chlorambucil (2 day)-Obinutuzumab (6 cycles)

Regimen

- CLL – Chlorambucil (2 day)-Obinutuzumab

Indication

- The first line treatment of CLL in those with co-morbidities making them unsuitable for full dose fludarabine therapy or bendamustine treatment.
- Palliative intent

Toxicity

Drug	Adverse Effect
Chlorambucil	Neutropenia, thrombocytopenia, anaemia, nausea, vomiting, diarrhoea, mouth ulceration, rash
Obinutuzumab	Infusion related reactions, Progressive multifocal leukoencephalopathy (PML), cardiac toxicity, thrombocytopenia, neutropenia, tumour lysis syndrome

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

Monitoring

- FBC on day one, optional on days eight and fifteen of the cycle
- U&E and LFT prior to day one and optionally fifteen of the cycle
- Hepatitis B status prior to starting treatment. Patients with positive hepatitis B serology should consult a liver disease expert before the start of treatment and should be monitored and managed following local medical standards to prevent hepatitis re-activation
- Consider uric acid and bone profile prior to cycle one in those considered at risk of tumour lysis syndrome

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.

At the start of each cycle the neutrophil count should be equal to or greater that $1x10^9$/L and the platelets equal to or greater than $100x10^9$/L.

Toxicity	Obinutuzumab Dose	Chlorambucil Dose (% of previous dose)
Grade 3 or 4 haematological toxicity, febrile neutropenia or thrombocytopenic bleeding that delays treatment by less than 4 weeks	Hold until the above parameters are met then restart at usual dose.	Hold until the above parameters are met. 1st episode: upon recovery restart at 75% 2nd episode: upon recovery restart at 50% 3rd episode: discontinue
Grade 3 or 4 haematological toxicity that delays treatment by more than 4 weeks	Discontinue	Discontinue

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.

The safety and efficacy of obinutuzumab in patients with impaired hepatic function has not been established.

Renal Impairment

Dose adjustment is not considered necessary for either chlorambucil or obinutuzumab in those with mild to moderate renal impairment.

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

Other

Toxicity	Obinutuzumab dose	Chlorambucil dose (% previous dose)
Grade 2 or 3 related organ/non- haematological toxicity	Hold until less than or equal to grade 1	Hold until less than or equal to grade 1
Grade 2 non haematological toxicity that delays treatment by more than 4 weeks	Discontinue	Discontinue
Grade 4 related organ/non- haematological toxicity, severe haemorrhage, severe skin reaction, pneumonitis, severe arrhythmias or other severe cardiovascular events	Discontinue	Discontinue
Viral hepatitis or other serious infections; reactivation of hepatitis B	Discontinue	Discontinue

Obinutuzumab

Progressive Multifocal Leukoencephalopathy

Progressive multifocal leukoencephalopathy (PML) has been reported in patients treated with obinutuzumab. The diagnosis of PML should be considered in any patient presenting with new-onset or changes to pre- existing neurologic manifestations. The patient should be referred to a neurologist for the evaluation and treatment of PML.

Infusion Reactions

Obinutuzumab administration is associated with infusion related reactions, particularly during the first cycle.

Most frequently reported symptoms associated with an infusion related reaction were nausea, chills, hypotension, pyrexia, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia, and diarrhoea. Respiratory and cardiac symptoms such as bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema and atrial fibrillation have also been reported.

Anaphylaxis has been reported during administration of obinutuzumab. If a hypersensitivity reaction is suspected during infusion (e.g. symptoms typically occurring after previous exposure and very rarely with the first infusion), the infusion must be stopped and treatment permanently discontinued.

Appropriate pre-medication must be administered before each infusion to reduce the risk of infusion related reactions.

Infusion related reactions should be treated as described in the table below.

Toxicity Grade	Obinutuzumab	Chlorambucil Dose (% of previous dose)
1-2	Reduce the infusion rate by half and treat symptoms. Restart the infusion once symptoms have resolved. Escalate infusion rate as tolerated at increments appropriate for treatment	No change
1episode of grade 3	Hold infusion and treat the symptoms. Restart the infusion once the symptoms have resolved at no more than half the previous rate. Escalate the infusion rate as tolerated at increments appropriate for the treatment dose (see below) The day 1 (cycle 1) infusion rate may be increased back up to 25mg/hr after 60 minutes, but not increased further	No change
2nd episode of grade 3 (during same or subsequent infusion)	Infusion must be stopped and therapy must be permanently discontinued	Discontinue
Grade 4 or acute life threatening respiratory reactions	Infusion must be stopped and therapy must be permanently discontinued	Discontinue

Tumour Lysis Syndrome (TLS)

Tumour lysis syndrome (TLS) has been reported with obinutuzumab. Patients who are considered to be at risk of TLS (e.g. patients with a high tumour burden and/or a high circulating lymphocyte count (greater than $25x10^9$/L) and/or renal impairment (CrCl less than 70 ml/min) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of allopurinol or a suitable alternative such as rasburicase starting 12-24 hours prior to the infusion. All patients considered at risk should be carefully monitored during the initial days of treatment with a special focus on renal function, potassium, and uric acid values. Any additional guidelines according to standard practice should be followed. For example the BTS guidelines. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Regimen

28 day cycle for 6 cycles for treatment and 12 cycles for maintenance (6 cycles will be set in ARIA)

Please note that if you add additional cycles to this regimen using the pen icon you must do this as starting from the last cycle of treatment (eg cycle 6). If you choose start from cycle one then the first cycle with the different doses of obintuzumab will be added.

Cycle 1

Drug	Dose	Days	Administration
Chlorambucil	0.5mg/kg	1, 15	Oral
Obinutuzumab	100mg	1	Intravenous infusion in 100ml sodium chloride 0.9% at a rate of 25mg/hour (over 240 minutes)*
Obinutuzumab	900mg	2	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 50mg/hour*
Obinutuzumab	1000mg	8, 15	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Chlorambucil	0.5mg/kg	1, 15	Oral
Obinutuzumab	1000mg	1	Intravenous infusion in 250ml sodium chloride 0.9% at a rate of 100mg/hour*

*Please see administration information below for infusion rates

Dose Information

- Chlorambucil is available as 2mg film-coated tablets.

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) or the full dose taken at night if nausea or vomiting is problematic.
- The film-coated chlorambucil tablets should not be crushed or dissolved prior to administration.
- Obinutuzumab standard infusion rates, in the absence of reactions are as follows;

Cycle	Day of Treatment	Rate of Infusion
1	Day 1 (100mg in 100ml)	Administer at 25mg/hour (over 240 minutes). Do not increase the rate
1	Day 2 (or day 1 continued) (900mg in 250ml)	Start the administration at 50mg/hour The rate of the infusion can be escalated in increments of 50 mg/hour every 30 minutes to a maximum rate of 400mg/hour
1	Day 8, 15 (1000mg in 250ml)	Infusions can be started at a rate of 100mg/hour and increased by 100 mg/hour increments every 30 minutes to a maximum of 400mg/hour
2 onwards	All days (1000mg in 250ml)	Infusions can be started at a rate of 100mg/hour and increased by 100mg/hour increments every 30 minutes to a maximum of 400mg/hour

The recommended dose of obinutuzumab is 1000 mg administered over day 1 and day 2, and on day 8 and day 15 of the first treatment cycle. Two infusion bags should be prepared for the infusion on days 1 and 2 (100 mg for day 1 and 900 mg for day 2).

If the first infusion (100mg) is completed without modifications of the infusion rate or interruptions, the second bag may be administered on the same day (no dose delay necessary, no repetition of premedication), provided that appropriate time, conditions and medical supervision are available throughout the infusion. If there are any modifications of the infusion rate or interruptions during the first 100 mg the second infusion (900mg) must be administered the following day.

Additional Treatment

- Antiemetics 15-30 minutes prior to chemotherapy

  - metoclopramide 10mg three times a day when required

- Premedication for obinutuzumab infusion reactions

  - sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

  then as follows;

Pre-medication (60 minutes prior to obinutuzumab)	Cycle 1 days 1 and 2	Cycle 1 days 8 and 15 and Cycles 2, 3, 4, 5, 6		
	All Patients	Patients without infusion related reactions	Patients with grades 1-2 infusion related reactions	Patients with a grade 3 infusion related reactions or with a lymphocyte count greater than $25x10^9/L$
Methylprednisolone sodium succinate 80mg intravenous	√			√
Chlorphenamine 10mg intravenous	√		√	√
Paracetamol 1000mg oral	√	√	√	√

On an as required basis;

- chlorphenamine 10mg intravenous for infusion reactions
- lorazepam 1mg oral for rigors
- methylprednisolone sodium succinate 80mg intravenous for infusion reactions
- paracetamol 1000mg oral for pyrexia
- pethidine 25mg intravenous in 10ml sodium chloride 0.9% over 5 minutes for rigors following a verbal confirmation to administer from a doctor.

- Allopurinol 300mg oral starting two days prior to day one cycle one for 7 days in total (not included in ARIA). Rasburicase may be required for high risk individuals.

- Anti-infective prophylaxis as follows;

  - consider aciclovir 400mg twice a day oral (consultants discretion, not included on ARIA)

- Mouthwashes as per local formulary

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.

- Hypotension may occur during obinutuzumab intravenous infusions. Therefore, withholding of antihypertensive treatments should be considered for 12 hours prior to and throughout each obinutuzumab infusion and for the first hour after administration. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine

Coding

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

References
1. Goede V, Fisher K, Busch et al. Obinutuzumab plus chlorambucil in patients with chronic lymphocytic leukemia and co-existing conditions. N Engl J Med 2014; 370 (12): 1101-1110.
2. Dawson K, Moran M, Guindon K et al. Managing infusion related reactions for patients with chronic lymphocytic leukemia receiving obinutuzumab . Clin J Oncol Nursing 2016; 20 (2): 41-48

REGIMEN SUMMARY

Chlorambucil (2 day)-Obinutuzumab (6 cycles)

Cycle 1

Day 1

1. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

2. Chlorphenamine 10mg intravenous
   Administration Instructions
   Administer 60 minutes prior to obinutuzumab

3. Methylprednisolone sodium succinate 80mg intravenous
   Administration Instructions
   Administer 60 minutes prior to obinutuzumab

4. Paracetamol 1000mg oral
   Administration Instructions
   Please check if the patient takes regular paracetamol for pain control and take dose into account
   Administer 60 minutes prior to obinutuzumab

5. Obinutuzumab 100mg intravenous infusion in 100ml sodium chloride 0.9% over 240 minutes
   Administration Instructions
   Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

6. Chlorphenamine 10mg when required for infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions

7. Lorazepam 1mg oral when required for rigors
   Administration Instructions
   For the relief of rigors

8. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
   Administration Instructions
   For the relief of infusion related reactions

9. Paracetamol 1000mg oral when required for pyrexia
   Administration Instructions
   For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

10. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 2

11. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

12. Chlorphenamine 10mg intravenous
    Administration Instructions

Administer 60 minutes prior to obinutuzumab

13. Methylprednisolone sodium succinate 80mg intravenous
    Administration Instructions
    Administer 60 minutes prior to obinutuzumab

14. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account
    Administer 60 minutes prior to obinutuzumab

15. Obinutuzumab 900mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

16. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

17. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

18. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

19. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

20. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 8

21. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

22. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count than $25x10^9/L$

23. Methylprednisolone sodium succinate 80mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction

24. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

25. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

26. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

27. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

28. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

29. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

30. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Day 15

31. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

32. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction or with a lymphocyte count greater than $25x10^9$/L

33. Methylprednisolone sodium succinate 80mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reaction

34. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

35. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride over 240 minutes
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

36. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

37. Lorazepam 1mg oral when required for rigors
    Administration Instructions
    For the relief of rigors

38. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

39. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

40. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines (day one only)

41. Chlorambucil 0.5mg/kg on days 1 and 15 only oral
    Administration Information
    Oral chemotherapy. Please supply day 1 and day 15 on day 1.

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

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

42. Metoclopramide 10mg three times a day when required for the relief of nausea
    Administration Instructions
    Please supply 28 tablets or nearest original pack size

Cycle 2, 3, 4, 5, 6 Day 1

43. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes

44. Chlorphenamine 10mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 1 or above infusion related reaction

45. Methylprednisolone sodium succinate 80mg intravenous when required for infusion related reactions
    Administration Instructions
    Please refer to the protocol. Administer 60 minutes prior to obinutuzumab if there has been a grade 3 or above infusion related reactions

46. Paracetamol 1000mg oral
    Administration Instructions
    Please check if the patient takes regular paracetamol for pain control and take dose into account. Administer 60 minutes prior to obinutuzumab

47. Obinutuzumab 1000mg intravenous infusion in 250ml sodium chloride 0.9%
    Administration Instructions
    Please refer to the protocol for information regarding infusion rates and infusion related reactions. These may be increased according to tolerance as per the protocol.

48. Chlorphenamine 10mg when required for infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions or with a lymphocyte count greater than $25x10^9$/L

49. Lorazepam 1mg oral when required for rigors
    Administration Instructions

For the relief of rigors

50. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
    Administration Instructions
    For the relief of infusion related reactions

51. Paracetamol 1000mg oral when required for pyrexia
    Administration Instructions
    For the relief of pyrexia. Please check if the patient takes regular paracetamol for pain control and take dose into account

52. Pethidine 25mg intravenous bolus in 10ml sodium chloride 0.9% over 5 minutes for the relief of rigors
    Administration Instructions
    For the relief of rigors following a verbal confirmation to administer from a doctor

Take Home Medicines (day one only)

53. Chlorambucil 0.5mg/kg on day 1 and 15 only oral
    Administration Information
    Oral chemotherapy. Please supply day 1 and day 15 on day 1.

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

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

55. Metoclopramide 10mg three times a day when required for the relief of nausea
    Administration Instructions
    Please supply 28 tablets or nearest original pack size

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	October 2017	Hepatitis B statement updated. TLS information added	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
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.