Chemotherapy Protocol

Non-Hodgkin Lymphoma

Bendamustine-Obinutuzumab

Regimen

- NHL – Bendamustine-Obinutuzumab

Indication

- Obinutuzumab in combination with bendamustine followed by obinutuzumab maintenance is recommended as an option for treating adults with follicular lymphoma that did not respond or progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.

Toxicity

Drug	Adverse Effect
Bendamustine	Transfusion related GVHD, Gastro-intestinal disturbances, fatigue, insomnia, cardiac dysfunction, hypotension/hypertension, hypersensitivity reactions, hypokalaemia.
Obinutuzumab	Infusion related reactions, Progressive multifocal leukoencephalopathy (PML), cardiac toxicity, thrombocytopenia, neutropenia, tumour lysis syndrome

Patients treated with bendamustine 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.

Monitoring

- FBC on day one of the first six cycles, optional on days eight and fifteen of the first cycle
- U&E and LFT prior to day one of the first six cycles and optionally fifteen of the first cycle. Ensure close monitoring of potassium levels in patients with pre-existing cardiac disorders whist on bendamustine.
- 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 (80mg/L). **Irradiated blood products must be used.**

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.

There are no dose reduction for obinutuzumab based on haematological parameters.

Bendamustine may be adjusted according to consultant advice. The following is for guidance only.

Neutrophils ($x10^9$/L)	**Dose Modifications**
More than 1	100%
0.5-1	Delay until recovery and then give 100%
Less than 0.5 or febrile neutropenia	1st occurrence - delay until recovery and give 75% of the original dose 2nd occurrence - delay until recovery and give 50% of the original dose
Platelets ($x10^9$/L)	**Dose Modifications**
More than 100	100%
25-100	Delay until recovery and give 100%
less than 25 or bleeding	1st occurrence - delay until recovery and give 75% of the original dose 2nd occurrence - delay until recovery and give 50% of the original dose

Hepatic Impairment

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

Drug	Bilirubin (μmol/L)	Dose (% of original dose)
Bendamustine	less than 21	100%
	21-51	70%
	more than 51	no information

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

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bendamustine	more than 10	100%
	10 or less	no information

Dose adjustment is not considered necessary for 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

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.

Bendamustine

Skin

Cases of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis have been reported in patients who received bendamustine and allopurinol simultaneously. If patients experience any skin reactions during treatment, they should be monitored closely and, in the case of any suspicion of the skin reaction evolving to a serious muco-cutaneous reaction, treatment with bendamustine should be withheld until complete resolution of the event or discontinued. Other potential causes of skin toxicity should be evaluated and suspected agents discontinued accordingly.

Infusion Reactions

Infusion reactions to bendamustine hydrochloride have occurred commonly in clinical trials. Symptoms are generally mild and include fever, chills, pruritus and rash. In rare instances severe anaphylactic and anaphylactoid reactions have occurred. Patients

must be asked about symptoms suggestive of infusion reactions after their first cycle of therapy. Measures to prevent severe reactions, including antihistamines, paracetamol and corticosteroids must be considered in subsequent cycles in patients who have previously experienced infusion related reactions.

Obinutuzumab

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

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. Patients with a high tumour burden and / or high circulating lymphocyte count (greater than $25x10^9$/L may be at increased risk of severe infusion related reactions (this has been particularly noted in the CLL setting).

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
1-2	Reduce the infusion rate by 50% and treat symptoms. Restart the infusion once symptoms have resolved. Escalate infusion rate as tolerated at increments appropriate for treatment
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
2nd episode of grade 3 (during same or subsequent infusion)	Infusion must be stopped and therapy must be permanently discontinued
Grade 4 or acute life threatening respiratory reactions	Infusion must be stopped and therapy must be permanently discontinued

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 British Society for Haematology 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

Cycle 1

Drug	Dose	Days	Administration
Bendamustine	$90mg/m^2$	1, 2	Intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
Obinutuzumab	1000mg	1, 8, 15	Intravenous infusion in 250ml sodium chloride 0.9% (see administration information for the rate of administration

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Bendamustine	90mg/m^2	1, 2	Intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes
Obinutuzumab	1000mg	1	Intravenous infusion in 250ml sodium chloride 0.9% (see administration information for the rate of administration

This is followed by maintenance treatment. The maintenance obinutuzumab will set as a separate protocol in ARIA.

Cycle 7 – 18 inclusive (1-12 inclusive in ARIA)

56 Day Cycle

This will be set as a separate regimen in ARIA

Drug	Dose	Days	Administration
Obinutuzumab	1000mg	1	Intravenous infusion in 250ml sodium chloride 0.9% (see administration information for the rate of administration

Dose Information

- Bendamustine will be dose banded according to the national dose bands (2.5mg/ml)

Administration Information

Extravasation

- Bendamustine – vesicant
- Obinutuzumab – non-vesicant

Other

Obinutuzumab standard infusion rates, in the absence of reactions are as follows;

Cycle	Day of Treatment	Rate of Infusion (Obinutuzumab)
1	Day 1	Start the administration at 50mg/hour The rate of the infusion can be escalated in increments of 50mg/hour every 30 minutes to a maximum rate of 400mg/hour
1	8, 15	If an infusion related reaction at Grade 1 or below occurred during the previous infusion when the final infusion rate was 100mg/hr or faster, infusions can be started at a rate of 100mg/hr and increased by 100mg/hr increments every 30 minutes to a maximum of 400mg/hr. If the patient experienced an infusion related reaction of Grade 2 or higher during the previous infusion administer at 50mg/hr. The rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.
2	All days	

Additional Treatment

- Antiemetics

  15-30 minutes prior to bendamustine on day 1

  - ondansetron 8mg oral or intravenous

  As take home medication on day 1

  - metoclopramide 10mg three times a day when required oral
  - ondansetron 8mg twice a day oral for 3 days

  On day 2 please ensure the patient has taken the ondansetron at home

- 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 day 1	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.

- Consider anti-infective prophylaxis with;

  - aciclovir 400mg twice a day oral (consultants discretion, not included on ARIA)
  - co-trimoxazole 960mg once a day on Monday, Wednesday and Friday oral whilst on bendamustine

  - Patients at high risk of tumour lysis syndrome (TLS) should be started on allopurinol 300mg once a day for 7 days. The course should be kept as short as possible to reduce the risk of Stevens-Johnson syndrome and toxic epidermal necrolysis associated with concomitant bendamustine and allopurinol use. Allopurinol should not be used where the risk of TLS is deemed low. High risk patients may require rasburicase.

  - 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.

Additional Information

- Bendamustine metabolism involves cytochrome P450 (CYP) 1A2 isoenzyme. Therefore, the potential for interaction with CYP1A2 inhibitors such as fluvoxamine, ciprofloxacin, aciclovir and cimetidine exists.

- 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 – X

- Delivery – X

References
1. Sehn LH et al. Obinutuzumab plus bendamustine versus bendamustine monotherapy in patients with rituximab-refractory indolent non-Hodgkin lymphoma (GADOLIN): a randomised, controlled, open-label, multicentre, phase 3 trial. Lancet Oncol (2016); 17(8): 1081-1093.

REGIMEN SUMMARY

Bendamustine-Obinutuzumab

Cycle 1 Day One

1. Warning – Check blood transfusion status
   Administration Instructions
   Patients treated with bendamustine 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 to carry with them at all times.

2. Ondansetron 8mg oral or intravenous

3. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

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

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

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

7. 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

8. 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.

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

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

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

12. 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

13. 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

Cycle 1 Day Two

14. Warning – Check supportive medication taken
    Administration Instructions
    Please ensure that the patient has taken ondansetron 8mg oral on the morning of treatment. If not please administer ondansetron 8mg oral or intravenous 15-30 minutes prior to chemotherapy.

15. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Take home medicines (day 1 only)

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

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

18. Allopurinol 300mg once a day for 7 days
    Administration Instructions
    Please refer to the protocol for recommendations on the prevention and treatment of tumour lysis syndrome. Individuals at high risk may require rasburicase.

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

Cycle 1 Day Eight and Fifteen

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

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

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

23. 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

24. 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.

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

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

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

For the relief of infusion related reactions

28. 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

29. 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

Cycle 2, 3, 4, 5 Day One

30. Ondansetron 8mg oral or intravenous

31. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

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

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

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

35. 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

36. 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.

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

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

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

40. 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

41. 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

Cycle 2, 3, 4, 5 Day Two

42. Warning – Check supportive medication taken
    Administration Instructions
    Please ensure that the patient has taken ondansetron 8mg oral on the morning of treatment. If not please administer ondansetron 8mg oral or intravenous 15-30 minutes prior to chemotherapy.

43. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Take home medicines (day 1 only)

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

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

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

Cycle 6 Day One

1. Warning – Consider Maintenance
   Administration Instructions
   Please consider if patients require maintenance obinutuzumab. This is a separate protocol on ARIA.

2. Ondansetron 8mg oral or intravenous

3. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

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

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

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

7. 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

8. 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.

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

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

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

12. 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

13. 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

Cycle 6 Day Two

14. Warning – Check supportive medication taken
    Administration Instructions
    Please ensure that the patient has taken ondansetron 8mg oral on the morning of treatment. If not please administer ondansetron 8mg oral or intravenous 15-30 minutes prior to chemotherapy.

15. Bendamustine 90mg/m^2 intravenous infusion in 500ml sodium chloride 0.9% over 30 minutes

Take home medicines (day 1 only)

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

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

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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	June 2018	Chlorambucil removed from table on page 5 BTS changed to British Society of Haematology Administration information updated Disclaimer updated	Dr Deborah Wright Pharmacist	Debra Robertson Pharmacist
1.1	April 2018	Obinutuzumab infusion volume changed to 250ml in regimen table.	Dr Deborah Wright Pharmacist	Debra Robertson Pharmacist
1	October 2017	None	Dr Deborah Wright Pharmacist	Dr Rob Lown 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. These protocols should be used in conjunction with other references such as the Summary of Product Characteristics and relevant published papers.