Chemotherapy Protocol

Non-Hodgkin Lymphoma

Obinutuzumab (Maintenance)

Regimen

- NHL – Obinutuzumab (Maintenance)

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
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, U&E and LFT prior to day one of each cycle

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).

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.

Hepatic Impairment

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

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 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.

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. This is maintenance treatment so patients should have already received obinutuzumab.

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 half 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. This is a maintenance regimen so the risk is less than with induction treatment. 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

56 Day Cycle for 12 cycles

This maintenance regimen follows on from six cycles of bendamustine and obinutuzumab.

Drug	Dose	Days	Administration
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

Administration Information

Extravasation

- Obinutuzumab – non-vesicant

Other

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

Cycle	Day of Treatment	Rate of Infusion
1	Day 1	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
2 onwards	All days	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

Additional Treatment

- 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)

- 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

- 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

Obinutuzumab (Maintenance)

Day One

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 1000mg intravenous infusion in 250ml 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

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
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.