

Chemotherapy Protocol

Non-Hodgkin Lymphoma

Cyclophosphamide-Doxorubicin-Obinutuzumab-Prednisolone-Vincristine

(O-CHOP)

Regimen

- NHL – O-CHOP-Cyclophosphamide-Doxorubicin-Obinutuzumab-Prednisolone-Vincristine

Indication

- Obinutuzumab in combination with cyclophosphamide, doxorubicin, prednisolone and vincristine (CHOP) followed by obinutuzumab maintenance is recommended as an option for treating adults with untreated advanced follicular lymphoma (that is, first as induction treatment with chemotherapy then as maintenance therapy) provided the person has a Follicular Lymphoma International Prognostic Index (FLIPI) score of 2 or more
- WHO Performance Status 0, 1, 2

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis (rare), taste disturbances
Doxorubicin	Cardiomyopathy, alopecia, urinary discolouration (red),
Obinutuzumab	Infusion related reactions, progressive multifocal leukoencephalopathy (PML), cardiac toxicity, thrombocytopenia, neutropenia, tumour lysis syndrome
Prednisolone	Weight gain, gastro-intestinal disturbances, hyperglycaemia, CNS disturbances, cushingoid changes, glucose intolerance
Vincristine	Peripheral neuropathy, constipation, jaw pain

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 first six cycles, optional on days eight and fifteen of the first cycle
- Consider uric acid and bone profile prior to cycle one in those considered at risk of tumour lysis syndrome
- Ensure adequate cardiac function before starting therapy. Baseline LVEF should be measured in patients with a history of cardiac problems, cardiac risk factors or in the elderly. Discontinue doxorubicin if cardiac failure develops

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 than $1 \times 10^9/L$ and the platelets equal to or greater than $100 \times 10^9/L$.

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

Neutrophils ($\times 10^9/L$)	Dose Modifications (cyclophosphamide and doxorubicin)
Less than 1 on proposed day 1 of cycle (unless considered disease-related)	Delay therapy until neutrophils are greater than or equal to $1 \times 10^9/L$. Consider growth factors as secondary prophylaxis. Reconsider treatment options if not recovered after 14 days.
Grade 4 neutropenia or any febrile neutropenia following any cycle	Give growth factors with all subsequent cycles
Grade 4 neutropenia leading to infection despite G-CSF support	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 neutropenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment
Platelets ($\times 10^9/L$)	Dose Modifications (cyclophosphamide and doxorubicin)
Less than 100 on proposed day 1 of cycle (unless considered disease-related)	Delay therapy until platelets are greater or equal to $100 \times 10^9/L$. Reconsider treatment options if not recovered after 14 days.
Grade 4 thrombocytopenia following any cycle	Reduce dose of cyclophosphamide and doxorubicin by 50% for all subsequent cycles
Grade 4 thrombocytopenia recurs despite 50% dose reduction in cyclophosphamide and doxorubicin	Stop treatment

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.

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/L)	Dose (%of original dose)
Cyclophosphamide	Evidence suggests dose modification not necessary.			
Doxorubicin	less than *30	and	2-3xULN	75%
	*30-50	and/or	More than 3xULN	50%
	51-85		N/A	25%
	more than 85		N/A	omit
Vincristine	*30-51	or	60-180	50%
	more than 51	and	normal	50%
	more than 51	and	more than 180	omit

* Lower limit reflects local practice and may differ from published sources.

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide**	more than 20	100%
	10-20	75%
	less than 10	50%
Doxorubicin	less than 10	Consider dose reduction in severe renal failure
Vincristine	N/A	No dose adjustment needed

**Consider mesna in patients with pre-existing bladder disorders. Give an oral dose of 40% of the cyclophosphamide dose (rounded upwards to the nearest 400mg) at 0, 2 and 6 hours after the administration of the cyclophosphamide.

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.

Doxorubicin

Discontinue doxorubicin if cardiac failure develops

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 $25 \times 10^9/L$ 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 the symptoms. Restart the infusion once symptoms have resolved. Escalate infusion rate as tolerated at increments appropriate for treatment
1 episode 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 $25 \times 10^9/L$) 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 of Haematology guidelines. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

Vincristine

Reduce the vincristine dose to 1mg if an NCI-CTC grade 2 motor or grade 3 sensory neurological toxicity occurs. For higher toxicity grades or if toxicity increases despite dose reduction stop the vincristine.

Regimen

21 day cycle for 8 cycles

Cycle 1

Drug	Dose	Days	Administration
Cyclophosphamide	750mg/m ²	1	Intravenous bolus over 10 minutes
Doxorubicin	50mg/m ²	1	Intravenous bolus over 10 minutes
Obinutuzumab	1000mg	1, 8, 15	Intravenous infusion in 250ml sodium chloride 0.9% (see administration information for the rate of administration)
Vincristine	1.4mg/m ² (max 2mg)	1	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Prednisolone*	100mg	2, 3, 4, 5	Oral

Methylprednisolone is given as obinutuzumab pre-medication on day 1

Cycle 2, 3, 4, 5, 6

Drug	Dose	Days	Administration
Cyclophosphamide	750mg/m ²	1	Intravenous bolus over 10 minutes
Doxorubicin	50mg/m ²	1	Intravenous bolus over 10 minutes
Obinutuzumab	1000mg	1	Intravenous infusion in 250ml sodium chloride 0.9% (see administration information for the rate of administration)
Vincristine	1.4mg/m ² (max 2mg)	1	Intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
Prednisolone*	100mg	2, 3, 4, 5	Oral

Methylprednisolone is given as obinutuzumab pre-medication on day 1

Cycles 7, 8

Drug	Dose	Days	Administration
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 9 – 20 inclusive (1-12 inclusive in ARIA-maintenance therapy)

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](#)

- Cyclophosphamide will be dose banded according to the national dose bands (20PM)
- Doxorubicin will be dose banded according to the nationally dose bands (2PM)
- The maximum lifetime cumulative dose of doxorubicin is 450mg/m². However prior radiotherapy to mediastinal/pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m²
- Vincristine dose will be dose banded according to the national dose bands (1mg/ml)
- The maximum dose of vincristine is 2mg

[Administration Information](#)

[Extravasation](#)

- Cyclophosphamide – neutral
- Doxorubicin – vesicant
- Obinutuzumab – non-vesicant
- Vincristine - 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.
2	All days	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.

Additional Treatment

- Antiemetics

15-30 minutes prior to CHOP 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

- 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 $25 \times 10^9/L$
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.
- Patients at high risk of tumour lysis syndrome (TLS) should be started on allopurinol 300mg once a day for 7 days. Allopurinol should not be used where the risk of TLS is deemed low. Very high risk patients may require rasburicase.
 - Consider anti-infective prophylaxis in high risk patients, including:
 - aciclovir 400mg twice a day oral
 - co-trimoxazole 960mg once a day oral on Monday, Wednesday and Friday only
 - Mouthwashes according to local or national policy on the treatment of mucositis
 - Gastric protection with a proton pump inhibitor or a H₂ 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
- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

[Coding](#)

- Procurement – X
- Delivery – X

[References](#)

1. National Institute for Health and Clinical Excellence (2018). Technical Appraisal Guidance (TA 513). Obinutuzumab for untreated advanced follicular lymphoma. NICE:DOH

REGIMEN SUMMARY

O-CHOP-Cyclophosphamide-Doxorubicin-Obinutuzumab-Prednisolone-Vincristine

Cycle 1 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%
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. Ondansetron 8mg oral or intravenous
7. Doxorubicin 50mg/m² intravenous bolus over 10 minutes
8. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
9. Cyclophosphamide 750mg/m² intravenous bolus over 10 minutes
10. Chlorphenamine 10mg when required for infusion related reactions
Administration Instructions
For the relief of infusion related reactions
11. Lorazepam 1mg oral when required for rigors
Administration Instructions
For the relief of rigors
12. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
Administration Instructions
For the relief of infusion related reactions
13. 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
14. 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 1 only)

15. Prednisolone 100mg once a day in the morning for four days oral
Administration Instructions
Take 100mg each morning on days 2, 3, 4, 5 of the cycle
Take with or after food
16. Metoclopramide 10mg three times a day when required oral
Administration Instructions
Please supply 28 tablets or an original pack as appropriate
17. Ondansetron 8mg twice a day oral for 3 days starting on the evening of day one of treatment
Administration Instructions
To start on the evening of day one of the cycle
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.

Cycle 1 Day Eight and Fifteen

19. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes
20. Chlorphenamine 10mg intravenous
Administration Instructions
Administer 60 minutes prior to obinutuzumab
21. Methylprednisolone sodium succinate 80mg intravenous
Administration Instructions
Administer 60 minutes prior to obinutuzumab
22. 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
23. 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.
24. Chlorphenamine 10mg when required for infusion related reactions
Administration Instructions
For the relief of infusion related reactions
25. Lorazepam 1mg oral when required for rigors
Administration Instructions
For the relief of rigors
26. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
Administration Instructions
For the relief of infusion related reactions
27. 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

28. 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, 6 Day One

29. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes
30. Chlorphenamine 10mg intravenous
Administration Instructions
Administer 60 minutes prior to obinutuzumab
31. Methylprednisolone sodium succinate 80mg intravenous
Administration Instructions
Administer 60 minutes prior to obinutuzumab
32. 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
33. 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.
34. Ondansetron 8mg oral or intravenous
35. Doxorubicin 50mg/m² intravenous bolus over 10 minutes
36. Vincristine 1.4mg/m² (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes
37. Cyclophosphamide 750mg/m² intravenous bolus over 10 minutes
38. Chlorphenamine 10mg when required for infusion related reactions
Administration Instructions
For the relief of infusion related reactions
39. Lorazepam 1mg oral when required for rigors
Administration Instructions
For the relief of rigors
40. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
Administration Instructions
For the relief of infusion related reactions
41. 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
42. 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 1 only)

43. Prednisolone 100mg once a day in the morning for four days oral
Administration Instructions
Take 100mg each morning on days 2, 3, 4, 5 of the cycle
Take with or after food
44. Metoclopramide 10mg three times a day when required oral
Administration Instructions
Please supply 28 tablets or an original pack as appropriate
45. Ondansetron 8mg twice a day oral for 3 days starting on the evening of day one of treatment
Administration Instructions
To start on the evening of day one of the cycle

Cycle 7, 8 Day One

46. Warning – Consider Maintenance
Administration Instructions
Please consider if patients require maintenance obinutuzumab. This is a separate protocol on ARIA.
47. Sodium chloride 0.9% 500ml intravenous infusion over 60 minutes
48. Chlorphenamine 10mg intravenous
Administration Instructions
Administer 60 minutes prior to obinutuzumab
49. Methylprednisolone sodium succinate 80mg intravenous
Administration Instructions
Administer 60 minutes prior to obinutuzumab
50. 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
51. 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.
52. Chlorphenamine 10mg when required for infusion related reactions
Administration Instructions
For the relief of infusion related reactions
53. Lorazepam 1mg oral when required for rigors
Administration Instructions
For the relief of rigors
54. Methylprednisolone sodium succinate 80mg intravenous bolus when required for the relief of infusion related reactions
Administration Instructions
For the relief of infusion related reactions
55. 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

56. 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	June 2018	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.