**Chemotherapy Protocol**

## Non-Hodgkin Lymphoma

**Cyclophosphamide-Obinutuzumab-Prednisolone-Vincristine**

**(O-CVP)**

### Regimen

- NHL – O-CVP-Cyclophosphamide-Obinutuzumab-Prednisolone-Vincristine

### Indication

- Obinutuzumab in combination with cyclophosphamide, prednisolone and vincristine (CVP) 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 than 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 |
| 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

### 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 reductions for obinutuzumab based on haematological parameters.

| **Neutrophils ($x10^9$/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 $1x10^9$/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 ($x10^9$/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 $100x10^9$/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. | | | |
| | | | | |
| 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% |
| | | |
| 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.

*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 half<br>and treat symptoms. Restart the infusion once symptoms have resolved. Escalate infusion rate as tolerated at increments appropriate for treatment |
| First 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 $25x10^9$/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 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 (induction therapy)**

**Cycle 1**

| Drug | Dose | Days | Administration |
|---|---|---|---|
| Cyclophosphamide | 750mg/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/m2 (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 |
| Obinutuzumab | 1000mg | 1 | Intravenous infusion in 250ml sodium chloride 0.9% (see administration information for the rate of administration |
| Vincristine | 1.4mg/m2 (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 |

*Please see administration information below for infusion rates

Dose Information

- Cyclophosphamide will be dose banded according to the national dose bands (20PM)
- 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
- 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<br>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 100 mg/hr and increased by 100 mg/hr increments every 30 minutes to a maximum of 400 mg/hr.<br><br>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 CVP on day 1

  - ondansetron 8mg oral or intravenous

  As take home medication on day 1

  - metoclopramide 10mg three times a day when required oral

- 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.

- 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 $H_2$ 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

- The National Patient Safety Agency report NPSA/2008/RRR04 must be followed in relation to intravenous administration of vinca alkaloids.

## Coding

- Procurement – X70.8

- Delivery – X72.9

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-CVP-Cyclophosphamide-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. Vincristine 1.4mg/$m^2$ (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

8. Cyclophosphamide 750mg/$m^2$ intravenous bolus over 10 minutes

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

## Take home medicines (day 1 only)

14. 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

15. Metoclopramide 10mg three times a day when required oral
    Administration Instructions
    Please supply 28 tablets or an original pack as appropriate

16. 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

17. 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

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

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

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

21. 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

22. 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.

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

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

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

26. 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

27. 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**

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

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

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

31. 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

32. 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.

33. Ondansetron 8mg oral or intravenous

34. Vincristine 1.4mg/$m^2$ (max 2mg) intravenous bolus in 50ml sodium chloride 0.9% over 10 minutes

35. Cyclophosphamide 750mg/$m^2$ intravenous bolus over 10 minutes

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

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 1 only)

41. 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

42. Metoclopramide 10mg three times a day when required oral
    Administration Instructions
    Please supply 28 tablets or an original pack as appropriate

43. 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

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

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

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

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

48. 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

49. 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.

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

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

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

53. 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

54. 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<br>Pharmacist | Dr Rob Lown<br>Consultant<br>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.