Obinutuzumab and Chlorambucil

INDICATION

Adult patients with previously untreated chronic lymphocytic leukaemia who are unsuitable for full-dose fludarabine-based therapy and bendamustine-based therapy due to comorbidities. (NICE TA343 - BLUETEQ required)

TREATMENT INTENT

Disease Modification.

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Record stage of disease by clinical assessment: presence or absence of B symptoms, clinical extent of disease, FBC
3. Blood tests - CMV serology, CMV PCR, hepatitis B core antibody and hepatitis B surface Ag, hepatitis C antibody, EBV, VZV, HIV 1+2 after consent, TP53 mutation analysis, FBC, biochemistry, glucose
4. ECG +/-Echo if clinically indicated.
5. Record performance status (WHO/ECOG)
6. Record patient's height and weight.
7. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or undergone a hysterectomy.
8. Consent - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
9. Fertility - it is very important the patient understands the potential risk of infertility, all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
10. Hydration - in patients with bulk disease pre-hydrate with 1 liter sodium chloride 0.9% over 4 - 6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol.
11. Prescribe Allopurinol 300mg daily, if possible start 12-24 hours prior to chemotherapy and then continue for 7 days.
12. Withhold antihypertensive treatment 12 hours before, during and 1 hour after infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.
13. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
14. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures.
15. Treatment should be agreed in the relevant MDT.
DRUG REGIMEN

CYCLE 1

Day 1 & Day 15 CHLORAMBUCIL PO 0.5 mg/kg of body weight (2mg tablets)
on an empty stomach (at least one hour before meals or three hours after)

Day 1 Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone IV 20mg
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
OBINUTUZUMAB 100mg IV infusion in 100mL sodium chloride 0.9%

Day 2 Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone IV 20mg
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
OBINUTUZUMAB 900mg IV infusion in 250mL sodium chloride 0.9%

Day 8 & Day 15 Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone IV 20mg
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
OBINUTUZUMAB 1000mg IV infusion in 250mL sodium chloride 0.9%

CYCLE 2-6

Day 1 & Day 15 CHLORAMBUCIL PO 0.5 mg/kg of body weight (2mg tablets)
on an empty stomach (at least one hour before meals or three hours after)

Day 1 Pre-medication:
At least 60 minutes prior to infusion: Dexamethasone IV 20mg
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
OBINUTUZUMAB 1000mg IV infusion in 250mL sodium chloride 0.9%

*See premedication administration guidance summary table below.

PREMEDICATION:

Make sure that the patient receives adequate hydration. For cycle 1 on Days 1 & 2 administer 500mL normal saline 0.9% over 1 hour before administering Obinutuzumab.

<table>
<thead>
<tr>
<th>Pre-meds required</th>
<th>Cycle 1 Days 1 &amp; 2</th>
<th>Subsequent infusions Cycle 1 Days 8 &amp; 15 and Cycles 2-6</th>
<th>Patients without any IRR Symptoms</th>
<th>Patients with grades 1-2 (mild to moderate) IRR with the previous infusions</th>
<th>Patients with a grade 3 (severe) IRR with the previous infusion OR with a lymphocyte count &gt;25 x 10^9/L prior to next treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dexamethasone iv 20mg, completed at least 60 minutes prior to infusion</td>
<td>√</td>
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</tr>
<tr>
<td>Chlorphenamine iv 10mg, At least 30 minutes prior to infusion</td>
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<td>√</td>
</tr>
<tr>
<td>Paracetamol 1g PO, At least 30 minutes prior to infusion</td>
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</tbody>
</table>

*See premedication administration guidance summary table below.

Hydrocortisone should not be used as it has not been effective in reducing rates of IRR.

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[Authorised by Lymphoma Lead Dr. Graham Collins]
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INFUSION RATE

These are the recommended starting infusion rates assuming the patient has not experience infusion related reactions in the prior infusion; otherwise the infusion rate should be no more than half the previous rate.

**Cycle 1 Day 1:** Infuse at 25mg/hr over 4 hours. DO NOT increase the infusion rate.

**Cycle 1 Day 2:** The recommended initial rate for infusion is 50mg/hr; after the first 60 minutes, it can be escalated in 50mg/hr increments every 30 minutes to a maximum rate of 400mg/hr.

**Subsequent infusions:** subsequent doses of Obinutuzumab can be infused at an initial rate of 100mg/hr, and increased by 100mg/hr increments at 30-minute intervals, to a maximum of 400mg/hr.

Note: For guidance on infusion rates in the case of infusion related reactions. See adverse effects section below

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CYCLE FREQUENCY

Every 28 days for 6 cycles.

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RESTAGING

Re-staging is to be done by clinical assessment: presence or absence of B symptoms, clinical extent of disease, FBC.

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DOSE MODIFICATIONS

**Hematological toxicity**
- Treatment should be deferred if neutrophil count is <1.0 x 10^9/L and/or if platelet count is <100 x 10^9/L on Day 1 of each cycle unless secondary to bone marrow infiltration.
- Neutropenia is expected on Cycle 1 Day 8. Proceed with obinutuzumab dosing regardless of neutrophil count.
- No dose modification of Obinutuzumab is recommended.

**Hepatic/Renal Impairment**

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No dose reduction required. Monitor myelosuppression</td>
<td>Dose reduce in patients with gross hepatic dysfunction. Modify dose according to response. Once the tolerance is established after the first month of therapy the dosage should be modified according to response, e.g. level of haematological suppression.</td>
</tr>
</tbody>
</table>

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Obinutuzumab:

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<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
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<tbody>
<tr>
<td>No dose adjustment is required in patients with mild to moderate renal impairment (creatinine clearance (CrCl) 30-89 mL/min). The safety and efficacy has not been established in patients with severe renal impairment (CrCl &lt; 30 mL/min). Patients with renal impairment (CrCl &lt; 50 mL/min) are more at risk of IRRs, neutropenia and thrombocytopenia.</td>
<td>The safety and efficacy of Obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.</td>
</tr>
</tbody>
</table>

INVESTIGATIONS

FBC, U&Es, LFTs, glucose.

CONCURRENT MEDICATION

Allopurinol 300 mg daily. To start 12-24 hours before first cycle of chemotherapy and continue for 7 days. Allopurinol is normally only needed with the first cycle.

Withhold antihypertensive treatment 12 hours before, during and 1 hour after infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.

EMETIC RISK

Minimal to low

EXTRAVASATION RISK

Obinutuzumab: neutral

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

Chlorambucil

- Rash - well recognized complication usually widespread maculo-papular. Unusual if the patient is taking concomitant steroids.

Obinutuzumab

- Hypotension- may occur during Obinutuzumab intravenous infusions. Therefore, antihypertensive treatments should be withheld or 12 hours prior to and throughout and 1 hour after each infusion. Patients at acute risk of hypertensive crisis should be evaluated for the benefits and risks of withholding their anti-hypertensive medicine.
- Hematologic toxicity- neutropenia and thrombocytopenia.
- Worsening of pre-existing cardiac conditions
Infusion-related Toxicity:

- Obinutuzumab should be administered as per infusion protocol. Infusion-related reactions (IRRs) such as rashes, allergic and anaphylactic reactions or cytokine release syndrome (dyspnoea, bronchospasm and hypoxia, in addition to fever, chills, rigors, urticaria and angiooedema) should be treated promptly. It is recommended, that the infusion should be temporarily interrupted or slowed until the adverse event has subsided and then re-started at 50% of the previous dose.
- Ensure there is a doctor and experienced nurse available during administration of all doses on cycle 1 and subsequent doses if the patient previously reacted
- Monitor the patient closely during the infusion.
- Have symptomatic rescue medication readily available for administration in case of occurrence of IRRs.
- Have emergency resuscitation facilities available during infusion.
- Management of IRRs may require temporary interruption, reduction in the rate of infusion, or treatment discontinuations as outlined below:

<table>
<thead>
<tr>
<th>IRR grade</th>
<th>Recommendation</th>
</tr>
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<tbody>
<tr>
<td>Grade 4 (life-threatening)</td>
<td>- Infusion must be stopped and therapy must be permanently discontinued.</td>
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<tr>
<td>Grade 3 (severe)</td>
<td>- Infusion must be temporarily stopped and symptoms treated.</td>
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<tr>
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<td>- Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred).</td>
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<tr>
<td></td>
<td>- If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose.</td>
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<tr>
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<td>- The day 1 (cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.</td>
</tr>
<tr>
<td></td>
<td>- If the patient experiences a second occurrence of a grade 3 IRR, the infusion must be stopped and therapy permanently discontinued.</td>
</tr>
<tr>
<td>Grade 1-2 (mild to moderate)</td>
<td>- The infusion rate must be reduced and symptoms treated.</td>
</tr>
<tr>
<td></td>
<td>- Upon resolution of symptoms, the infusion can be restarted at no more than half the previous rate (the rate being used at the time that the IRR occurred).</td>
</tr>
<tr>
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<td>- If the patient does not experience any IRR symptoms, the infusion rate escalation can resume at the increments and intervals as appropriate for the treatment dose.</td>
</tr>
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<td>- The day 1 (cycle 1) infusion rate may be increased back up to 25 mg/hr after 1 hour, but not increased further.</td>
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TUMOUR LYSIS SYNDROME (TLS)

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 [> 25 x 10^9/L] and/or renal impairment [CrCl <70 mL/min]) should receive prophylaxis. Prophylaxis should consist of adequate hydration and administration of uricosurics (e.g. allopurinol), or a suitable alternative such as a urate oxidase (e.g. rasburicase) starting 12-24 hours prior to the infusion of Obinutuzumab as per tumour lysis protocol. All patients considered at risk should be carefully monitored during the initial days of treatment and should have a repeated test of renal function, potassium, and uric acid values 6 hrs after the infusion on day 1 and 2 of

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Lymphoma group

cycle 1. For treatment of TLS, correct electrolyte abnormalities, monitor renal function and fluid balance, and administer supportive care, including dialysis as indicated.

TREATMENT RELATED MORTALITY

2-3%

REFERENCES


Review

<table>
<thead>
<tr>
<th>Name</th>
<th>Revision</th>
<th>Date</th>
<th>Version</th>
<th>Review date</th>
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<tbody>
<tr>
<td>Cheuk-kie Jackie Cheung</td>
<td>Loading dose diluent modified</td>
<td>July 2018</td>
<td>1.2</td>
<td></td>
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<td>(Haematology Pharmacist)</td>
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<td></td>
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<tr>
<td>NSSSG Lymphoma Group</td>
<td>Annual protocol review</td>
<td>May 2019</td>
<td>1.3</td>
<td></td>
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<tr>
<td>Cheuk-kie Jackie Cheung</td>
<td>Addition of blueteq requirement as per NHSE</td>
<td>Oct 2019</td>
<td>1.4</td>
<td>May 2021</td>
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<tr>
<td>(Haematology Pharmacist)</td>
<td>circular 2090</td>
<td></td>
<td></td>
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<tr>
<td>Quality manager</td>
<td>Nursing care plan added</td>
<td>Sept 2020</td>
<td>1.5</td>
<td>May 2021</td>
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Nursing Care Plan: OBINUTUZUMAB AND CHLORAMBUCIL – CLL

**Indication:** CLL

**IMPORTANT:** Please make sure you have the right care plan for the patient as there are various similar combinations for CLL and FL treatments.

**Frequency:** 28 day cycles for 6 cycles.

**Alopecia:** potential hair thinning/patchy hair loss

**Emetic risk:** low.

**OBINUTUZUMAB:** monoclonal antibody

Administered IV on days 1&2 (in split doses), 8 and 15 of cycle 1. On day 1 of cycles 2-6.

**Classification of extravasation:** neutral

**Emetic risk:** low

**Side Effects:** nausea, chills, hypotension, pyrexia, vomiting, dyspnoea, flushing, hypertension, headache, tachycardia, diarrhoea, bronchospasm, larynx and throat irritation, wheezing, laryngeal oedema, atrial fibrillation, anaphylaxis – **infusion related reactions most common in the first 2 hours.**

Post Infusion reactions: hepatitis B reactivation, thrombocytopenia (occurring within 24 hours after the infusion), neutropenia, worsening of pre-existing cardiac conditions and tumorlysis.

- **Pre-meds: To be given 1 hour prior to Obinutuzumab.**
- **C1 D1:** all patients should receive IV Dexamethasone, IV Chlorphenamine and PO Paracetamol. Obinutuzumab can cause hypotension. Withhold anti-hypertensives 12 hours prior to the infusion and monitor throughout the patients treatment cycles. For cycle 1 day 1 administer 500mL sodium chloride 0.9% over 1 hour before administering Obinutuzumab (this is given after the premed so Obinutuzumab can be started as soon as prehydration finishes).

**Subsequent Infusions:**

- Patients without any IRR with the previous infusion should only receive PO paracetamol.
- Patients with grades 1-2 (mild to moderate – see protocol for description of reaction grades) IRR with the previous infusion should receive IV Chlorphenamine and PO Paracetamol. Patients with a grade 3 (severe) IRR with the previous infusion OR with a lymphocyte count >25 prior to the next treatment should receive IV Dexamethasone, IV Chlorphenamine and PO Paracetamol.
- **During the Infusion of Obinutuzumab:**
  - Ensure patient is treated on a bed (first cycle only, unless the patient has continued reactions)
  - **In DTU** (where the patient is visually in front of the nursing station with very close observation): Record baseline observations, after 30 minutes, after 1 hour and then if the patient reacts.
  - **On the ward:** record observations every 30 minutes for the first two and a half hours and then hourly. To have close observation.
  - Have anaphylaxis box nearby (include Dexamethasone and not Hydrocortisone in the kit) **Hydrocortisone must not be used as it has not been effective in reducing rates of IRR**
  - Increment drug infusion rate as per protocol. **Note there are different rates for first/second treatments.**
  - Educate patients re possible reactions and the importance of reporting any
Symptoms immediately.

- If patient reacts to Obinutuzumab:
  - Record observations.
  - Seek medical support.
  - Consider administration of IV Dexamethasone, IV Chlorphenamine, Oxygen, Salbutamol nebuliser depending on type and severity of reaction.

**Hydrocortisone must not be used as it has not been effective in reducing rates of IRR**

- Use adrenaline in case of anaphylactic shock and call 2222.

Document what time the reaction occurred, at what rate of the infusion/ the grade within the medical notes.

**CHLORAMBUCIL:** Alkylating agent
Administered orally
**Side effects:** bone marrow depression, nausea, skin rash, diarrhoea.