Obinutuzumab + Bendamustine

INDICATIONS

1st line treatment for follicular lymphoma with FLIPI score 2 or higher: (NICE TA513- BLUETEQ required)

Follicular lymphoma that did not respond or progressed up to 6 months after treatment with rituximab or a rituximab-containing regimen (NICE TA629- BLUETEQ required)

Note: There are other bendamustine protocols, ensure this is the correct one for a given patient.

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 – CT scan (neck, chest, abdomen and pelvis), and/or PET-CT scan, presence or absence of B symptoms, clinical extent of disease, consider bone marrow aspirate and trephine.
3. Blood tests – FBC, U&Es, LDH, urate, calcium, magnesium, LFTs, glucose, Igs, hepatitis B core antibody and hepatitis BsAg, hepatitis C antibody
4. Send a ‘group and save’ sample to transfusion and inform patient and transfusion laboratory that they will require irradiated blood products for all future transfusions. Ensure irradiation care is attached to the patient’s notes and copy given to the patient. See ‘Guidelines for the use of blood components in adult haematology’.
5. ECG +/-Echo if clinically indicated.
6. Record performance status (WHO/ECOG)
7. Record patient's height and weight.
8. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are postmenopausal, have been sterilised or undergone a hysterectomy.
9. 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.
10. 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.
11. 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.
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. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

CYCLE 1

Days 1  
**BENDAMUSTINE** 90mg/m² IV infusion in 500mL sodium chloride 0.9%
over 30-60 minutes

**Pre med:**
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV
500mL sodium chloride 0.9% over 1 hour before administering Obinutuzumab

**OBINUTUZUMAB** 1000mg IV infusion in 250mL sodium chloride 0.9%**

Day 2  
**BENDAMUSTINE** 90mg/m² IV infusion in 500mL sodium chloride 0.9%
over 30-60 minutes

Days 8 and 15  
**Pre med:**
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
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  
**BENDAMUSTINE** 90mg/m² IV infusion in 500mL sodium chloride 0.9%
over 30-60 minutes

Day 1 only  
**Pre med:**
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
At least 30 minutes prior to infusion: Paracetamol 1g PO and Chlorphenamine 10mg IV

**OBINUTUZUMAB** 1000mg IV infusion in 250mL sodium chloride 0.9%**

Day 2  
**BENDAMUSTINE** 90mg/m² IV infusion in 500mL sodium chloride 0.9%
over 30-60 minutes

CYCLE 7 onwards (Maintenance)

Every 2 months:  
**Pre med:**
At least 60 minutes prior to infusion: Dexamethasone 20mg IV
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” section below.
** See “Infusion Rate” section below.

PREMEDICATION:

- Make sure that the patient receives adequate hydration. For cycle 1 day 1 administer 500mL sodium chloride 0.9% over 1 hour before administering Obinutuzumab.

<table>
<thead>
<tr>
<th>Pre-meds required</th>
<th>Cycle 1 Days 1</th>
<th>Subsequent infusions</th>
<th>Cycle 1 Days 8 &amp; onwards</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All Patients</td>
<td>Patients without any IRR Symptoms</td>
<td>Patients with grades 1-2 (mild to moderate) IRR with the previous infusions</td>
</tr>
<tr>
<td>Dexamethasone 20mg IV², completed at least 60 minutes prior to infusion</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chlorphenamine 10mg IV. At least 30 minutes prior to infusion</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Paracetamol 1g PO. At least 30 minutes prior to infusion</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

²Hydrocortisone should not be used as it has not been effective in reducing rates of IRR (Infusion-related reaction).

INFUSION RATE

These are the recommended starting infusion rates assuming the patient has not experience infusion related reactions in the prior infusion. Upon symptom resolution of an IRR, the infusion rate should be no more than half the previous rate when the IRR occurred.

** Cycle 1 Day 1 **

Administer at 50mg/hr. The rate of infusion can be escalated in 50mg/hr increments every 30 minutes to a maximum of 400mg/hr.

** Subsequent infusions **

If no infusion related reactions occurred during the prior 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.

Note: For guidance on infusion rates in the case of infusion related reactions. See “Adverse Effects” section below.

CYCLE FREQUENCY

Induction: Every 28 days for 6 cycles. Maintenance: Every 2 months for up to 2 years (i.e. 12 infusions) Consider omitting maintenance for front line patients who have achieved deep remission with induction.

RESTAGING

CT (or PET/CT) at end of induction (6 courses of bendamustine + obinutuzumab)
DOSE MODIFICATIONS

Haematological 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 unless secondary to bone marrow infiltration.
- No dose modification of Obinutuzumab is recommended.
- Consider dose reduction of Bendamustine for haematological toxicity (consultant decision)

Hepatic/Renal Impairment

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>CrCl &gt; 10mL/min give 100% dose</td>
<td>Mild: Bili &lt; 20 micromol/L Give 100%</td>
</tr>
<tr>
<td></td>
<td>Moderate: Bili 20-51 micromol/L Give 70%</td>
</tr>
<tr>
<td></td>
<td>Severe: Bili &gt; 51 micromol/L No data</td>
</tr>
</tbody>
</table>

Bendamustine:
No dose adjustment is required in patients with mild to moderate renal impairment (CrCl 30-89 mL/min). The safety and efficacy has not been established in patients with severe renal impairment (CrCl < 30 mL/min).
Patients with renal impairment (CrCl < 50 mL/min) are more at risk of IRRs, neutropenia and thrombocytopenia.

Obinutuzumab:
- No dose adjustment is required in patients with mild to moderate renal impairment (CrCl 30-89 mL/min). The safety and efficacy has not been established in patients with severe renal impairment (CrCl < 30 mL/min).
- The safety and efficacy of Obinutuzumab in patients with impaired hepatic function has not been established. No specific dose recommendations can be made.

INVESTIGATIONS
FBC, U&Es, LFTs, glucose.

CONCURRENT MEDICATION

- Allopurinol (see ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS below) There have been rare skin reactions and other toxicities associated with the administration of allopurinol and bendamustine when given together. For those patients at a low risk of tumour lysis, allopurinol should be commenced following the administration of Bendamustine (i.e. day 3) at a dose of 300mg OD. Patients at intermediate risk (low grade NHL with disease bulk) of tumour lysis should receive allopurinol for 3 days prior to the administration of Bendamustine and for 5-7 days following Bendamustine.
- Aciclovir 200mg 3 times daily for the duration of induction period (Cycle 1-6 and maintenance)
- Co-trimoxazole 480 mg daily on Mon/ Wed/ Fri for induction and maintenance period (Consider reducing the dose to 480mg twice weekly during neutropenic periods)

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**

Moderate (during induction)
Low (maintenance)

**ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS**

For a full list of adverse effects and complications, refer to the summary of product characteristics.

Main side effects of Bendamustine: myelosuppression (dose titration may be required), hypersensitivity, liver enzyme rise, arrhythmia, possible risk of secondary malignancies.

NB: In the GALLIUM study there was an excess of opportunistic infections in the bendamustine arm compared with the CVP or CHOP arms. PCP prophylaxis should be administered during bendamustine treatment.

For patients at low risk of tumour lysis syndrome (TLS), avoid giving allopurinol on those days that the patient is receiving bendamustine. Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported in patients receiving bendamustine and allopurinol simultaneously.

Main side effects of Obinutuzumab: Infusion-related reaction, tumour lysis syndrome, neutropenia, thrombocytopenia, anaemia, hepatitis B reactivation, worsening of pre-existing cardiac condition, upper respiratory infections, diarrhoea and constipation.

**Infusion-related Toxicity:**

- Obinutuzumab should be administered as per infusion protocol. Infusion-related side-effects 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 rate.
- 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>
</thead>
<tbody>
<tr>
<td>Grade 4 (life threatening)</td>
<td>Infusion must be stopped and therapy must be permanently discontinued.</td>
</tr>
<tr>
<td>Grade 3 (severe)</td>
<td>Infusion must be temporarily stopped 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>
<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>
</tr>
</tbody>
</table>

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if the patient experiences a second occurrence of a Grade 3 IRR, the infusion must be stopped and therapy permanently discontinued

| Grade 1-2 (mild to moderate) | The infusion rate must be reduced and symptoms treated  
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)  
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. |

EXTRAVASTION RISK

Bendamustine: irritant / vesicant  
Obinutuzumab: neutral

TREATMENT RELATED MORTALITY

Up to 5% (as reported in GALLIUM and GADOLIN trials)

REFERENCES

NURSING CARE PLAN: OBINUTUZUMAB AND BENDAMUSTINE – FOLLICULAR LYMPHOMA

**Indication:** Follicular Lymphoma  
**IMPORTANT:** This care plan is only to be used for patients with FL. If patient is being treated for CLL the alternative care plan must be followed (Obinutuzumab and Chlorambucil).  
**Frequency:** 28 day cycles for the first 6 cycles then maintenance Obinutuzumab once every 2 months from cycle 7 onwards (for 2 years).  
**Alopecia:** hair thinning/patchy hair loss  
**Emetic risk:** moderate for cycles 1-6 then low for maintenance treatment.  
Send a group and save sample to blood transfusion and inform patient and laboratory that they will require irradiated blood products for all future transfusions. Give patient an irradiated blood product booklet and card

**OBINUTUZUMAB:** monoclonal antibody  
Administered IV on days 1, 8 and 15 of cycle 1. On day 1 of cycles 2-6. Every 2 months from cycle 7 as maintenance treatment (for 2 years).  
**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**

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Lymphoma group

- 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.

**BENDAMUSTINE**: Alkylating agent
Administered as IV infusion over 30-60 minutes on **days 1 and 2 of cycles 1-6**.

**Classification of extravasation**: vesicant
**Emetic risk**: moderate.
**Side effects**: tumour lysis syndrome, fever, chills, pruritis, rash, nausea and vomiting, myelosuppression, anorexia, diarrhoea, constipation, mucositis, fatigue, raised LFT’s, hypokalaemia, cardiac impairment, hypo/hypertension, insomnia, skin disorders, alopecia, amenorrhoea, risk of secondary malignancies.