Ofatumumab and Chlorambucil

INDICATION

Adult patients with previously untreated chronic lymphocytic leukaemia who are unsuitable for fludarabine and bendamustine based therapy. (NICE TA344)

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 BsAg, 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 each course of chemotherapy 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 litre sodium chloride 0.9% over 4 - 6 hours. Patients at high risk of tumour lysis refer to tumour lysis protocol.
11. Prescribe Allopurinol 300 mg daily, if possible start 24-48 hours prior to chemotherapy and then continue for 7 days.
12. Consider dental assessment / Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. For patients prescribed oral chemotherapy, ensure pre-chemotherapy counselling in line with NPSA recommendation and chemotherapy measures. Treatment should be agreed in the relevant MDT.
DRUG REGIMEN

CYCLE 1

Days 1 to 7  **CHLORAMBUCIL** PO 10 mg/m$^2$/day (2mg tablets)
on an empty stomach (at least one hour before meals or three hours after)

Day 1  **Pre-medication (30 min to 2 hrs prior to infusion):**
Chlorphenamine 10 mg IV, Paracetamol 1g PO and Dexamethasone 8mg IV.

**OFATUMUMAB** 300mg IV infusion in 1000mL Sodium Chloride 0.9%
See “Administration” section below for infusion rate.

Day 8  **Pre-medication (30 min to 2 hrs prior to infusion):**
Chlorphenamine 10 mg IV, Paracetamol 1g PO and Dexamethasone 8mg IV.

**OFATUMUMAB** 1000mg IV infusion in 1000mL Sodium Chloride 0.9%
See “Administration” section below for infusion rate.

CYCLE 2 - 12

Days 1 to 7  **CHLORAMBUCIL** PO 10 mg/m$^2$/day (2mg tablets)
on an empty stomach (at least one hour before meals or three hours after)

Day 1  **Pre-medication (30 min to 2 hrs prior to infusion):**
Chlorphenamine 10 mg IV, Paracetamol 1g PO and Dexamethasone 8mg IV.

**OFATUMUMAB** 1000mg IV infusion in 1000mL Sodium Chloride 0.9%
See “Administration” section below for infusion rate.

*Following the second infusion, if the patient does not experience a severe adverse drug reaction, pre-medication with a corticosteroid for subsequent infusions may either be reduced or omitted, at the discretion of the consultant.

CYCLE FREQUENCY

Every 28 days for a minimum of three cycles and for up to 12 cycles or until best response, with best response defined as a clinical response that does not improve with an additional three cycles of therapy.

RESTAGING

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

The starting rate of the initial infusion of 300 mg ofatumumab (0.3 mg/mL) should be 12 mL/hr. If no infusion reactions occur the infusion rate should be increased every 30 minutes, to a maximum of 400mL/hr. If this schedule is followed the duration will be approximately 4.5 hours for the first infusion.

If the first infusion has been completed without severe reaction, the subsequent infusions can start at a rate of 25mL/hr and should be increased every 30 minutes up to a maximum infusion rate of 400 mL/hr. If this schedule is followed, the infusion duration will be approximately 4 hours.

Infusion Rate for 1st Ofatumumab infusion

<table>
<thead>
<tr>
<th>Time Interval</th>
<th>Infusion Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – 30 minutes</td>
<td>12 mL/hr</td>
</tr>
<tr>
<td>31 – 60 minutes</td>
<td>25 mL/hr</td>
</tr>
<tr>
<td>61 – 90 minutes</td>
<td>50 mL/hr</td>
</tr>
<tr>
<td>91 – 120 minutes</td>
<td>100 mL/hr</td>
</tr>
<tr>
<td>121-150 minutes</td>
<td>200 mL/hr</td>
</tr>
<tr>
<td>151-180 minutes</td>
<td>300 mL/hr</td>
</tr>
<tr>
<td>181+ minutes</td>
<td>400 mL/hr*</td>
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</tbody>
</table>

* Maximum infusion rate for the first and subsequent infusions

If an infusion reaction develops, the infusion should be temporarily slowed or interrupted. Upon restart, the infusion rate should be half of the infusion rate at the time the infusion was paused. If, however, the infusion rate was 12 mL/hr before the pause, the infusion should be restarted at 12 mL/hr.

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 Ofatumumab is recommended

Hepatic/Renal Impairment

Chlorambucil:

<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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Ofatumumab:

<table>
<thead>
<tr>
<th>Renal impairment</th>
<th>Hepatic impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>No formal studies. No dose adjustment is recommended for mild to moderate renal impairment (creatinine clearance &gt;30 ml/min).</td>
<td>No formal studies. However, patients with hepatic impairment are unlikely to require dose modification.</td>
</tr>
</tbody>
</table>

INVESTIGATIONS

FBC, U&Es, LFTs, glucose.

CONCURRENT MEDICATION

| Allopurinol | Consider 300 mg daily for 7 days starting 24-48 hours before first cycle of chemotherapy. Allopurinol is normally only needed with the first cycle. |

EMETIC RISK

Minimal to low

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

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

Chlorambucil

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

Ofatumumab

Similar to rituximab including Hepatitis B reactivation.

Infusion-related Toxicity

Ofatumumab 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 dose.

TREATMENT RELATED MORTALITY

1-2%

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REFERENCES


