Alemtuzumab in Cutaneous Lymphoma

Indication: Treatment of patients with Cutaneous Lymphoma (Unlicensed use)
1. Disease control prior to Reduced Intensity Conditioning Stem Cell Transplant
2. Palliative disease control

Ensure patient has been registered to the Patient access programme.
Access to the programme may be denied for safety reasons
(including but not limited to the following)
- Known hypersensitivity to alemtuzumab or murine proteins
- Known HIV positive disease
- Active systemic infections
- Active second malignancies
- Pregnancy/ lactation

Regimen details:

**Cycle 1**
- Alemtuzumab SC 3mg D1
- Alemtuzumab SC 10mg D3 and D5

Thereafter
- Alemtuzumab SC 10mg Three times a week
  (usually Monday, Wednesday and Friday)

If Alemtuzumab is interrupted for $\geq 7$ days, restart at 3mg

Administration: Subcutaneous (Unlicensed use)

After the injection, monitor pulse, respiratory rate and Blood Pressure every 15 minutes during the first hour and then at one hour after the dose until at least 3 doses at the highest tolerated level. Record observations on a T.P.R. chart (see Comments, page 3)

If rigors develop, give Pethidine IV 25mg
In patients who develop a rash, give additional Chorphenamine every 4 hours as needed and consider premedicating with Histamine H$_2$ receptor antagonists

Premedication:
- Paracetamol PO 1g 30 min Pre-infusion
- Chlorphenamine IV 10mg 30 min Pre-infusion
- Hydrocortisone IV 100mg 30 min Pre first infusion and subsequent infusions if flu like symptoms

Frequency: Continued for up to 12 weeks

Discontinue treatment if:
- Complete Clinical Response (CCR). See Appendix 1
- Progressive Disease (PD). See Appendix 1
- No further improvement between 4 and 8 week assessment
- Neutrophils < 0.25 x 10$^9$/L, Platelets < 25 x 10$^9$/L (see Haematological toxicity)

Patients who have CCR can be retreated on relapse
Supportive medication: Prophylaxis (During and to continue for 2 months after Alemtuzumab or until CD4 > 200)
- Co-trimoxazole 480mg BD Three times a week (Mon, Wed, Fri)
- Aciclovir 400mg BD
- Posaconazole suspension 200mg TDS orally
- Allopurinol 300mg OD orally (100mg if renal impairment)
- Ciprofloxacin 500mg BD when Neutrophils < 0.5 x 10^9/L

Growth Factor support should be considered in neutropenic patients

**Irradiated Blood Products**

Blood and Platelets transfusion according to unit guidelines. All Blood transfusions must be with Cytomegalovirus (CMV) negative blood

Products must be irradiated, for life, as patients are at risk of Transfusion Associated Graft Versus Host Disease (TAGVHD). Ensure blood transfusion is notified and patient has received patient information leaflet “Information for patients needing irradiated blood” and Alert Card

**Extravasation:**

Non-vesicant

**Anti-emetics:**

Low emetogenic. Follow Local Anti-emetic Policy

**Pre-treatment Investigations:**

- History and Physical examination
- Clinical measurement of lymph nodes
- Skin Scoring and Clinical Photographs
- FBC&diff, U&E, LFT’s, Ca^2+, P, Glucose, Thyroid Stimulating Hormone, T4 Bone Marrow aspirate and Trephine, if FBC abnormal
- Lymphocyte subsets, Sezary count, Lactate Dehydrogenase
- CXR, CT scan Neck, Chest, Abdomen and Pelvis
- Path review to confirm CD 52+ expression
- Human T-cell Lymphotropic Virus, Human Immunodeficiency Virus (HIV)
- CMV IgG, Varicella Zoster Virus IgG, Herpes Simplex Virus IgG, Hepatitis C Virus IgG
- Hepatitis B surface Ag, Antibody to Hepatitis B core Ag, Antibody to Hepatitis B surface Ag
- Baseline Polymerase Chain Reaction (PCR) analysis for CMV positive patients
- Toxoplasma IgG
- Syphilis serology, Epstein-Barr Virus serology

**Regular investigation:**

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>FBC &amp; diff</td>
<td>Prior to each dose</td>
</tr>
<tr>
<td>Lymphocyte subsets</td>
<td>Weekly</td>
</tr>
<tr>
<td>LFTs</td>
<td>Weekly</td>
</tr>
<tr>
<td>U&amp;Es</td>
<td>Weekly</td>
</tr>
<tr>
<td>Glucose</td>
<td>Weekly</td>
</tr>
<tr>
<td>Uric acid</td>
<td>Weekly</td>
</tr>
<tr>
<td>PCR for CMV viral load in CMV positive patients</td>
<td>Weekly (see CMV Monitoring)</td>
</tr>
<tr>
<td>Clinical review (skin, lymph nodes, side effects)</td>
<td>Every 2 weeks</td>
</tr>
<tr>
<td>CT scan</td>
<td>Every 4 weeks</td>
</tr>
<tr>
<td>Sezary Count</td>
<td>After 4th dose and then at 4 weeks, 8 weeks and 12 weeks</td>
</tr>
</tbody>
</table>

Reason for Update: Patient access programme set up
Approved by Consultant Clinical Oncologist: Stephen Morris

Version: 1.1                      Date: 11/12/2012
Supersedes: All other versions    Checked by (Network Pharmacist): Jacky Turner
Prepared by: Maria Teresa Pacheca Palomar    Date: 20/11/2012
update by S.Eestila Oct-12
CMV Monitoring

Baseline PCR for CMV
Weekly PCR for CMV IgG in CMV positive patients
In the presence of CMV reactivation:
  • Discontinue Alemtuzumab
  • Start IV Gangciclovir 5mg/kg twice daily
  • If asymptomatic continue for 7-14 days or until 2 consecutive negative tests
  • If symptomatic continue for 14-21 days or until 2 consecutive negative tests

In asymptomatic patients an alternative is oral Valganciclovir 900mg bd for 14-21 days. Consultant decision only

In CMV negative patients, repeat CMV IgG if Fever of Unknown origin

After discontinuation of Alemtuzumab, monitor:

<table>
<thead>
<tr>
<th>Test</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>U&amp;E/Cr</td>
<td>Every 2 weeks in the first month and then Monthly</td>
</tr>
<tr>
<td>CMV viral load in CMV positive patients</td>
<td>Monthly, for 6 months</td>
</tr>
<tr>
<td>Thyroid Function</td>
<td>Monthly</td>
</tr>
<tr>
<td>Sezary Counts</td>
<td>Monthly</td>
</tr>
</tbody>
</table>

Comments: Alemtuzumab – Injection related events
Alemotuzumab has been associated with injection related events including hypotension, rigors, fever, shortness of breath, bronchospasm, chills and/or rash. In post-marketing reports, the following serious infusion-related events were reported: syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, cardiac arrhythmias, myocardial infarction and cardiac arrest. The cardiac adverse events have resulted in death in some cases. In order to ameliorate or avoid infusion related events, patients should be pre medicated (see Premedication) with Paracetamol, Chlorphenamine and Hydrocortisone prior to treatment. In addition, Alemtuzumab should be initiated at a low dose with gradual escalation to the effective dose. Careful monitoring of blood pressure and hypotensive symptoms is recommended especially in patients with ischaemic heart disease and in patients on antihypertensive medications. If therapy is interrupted for 7 or more days, Alemtuzumab should be re instituted with gradual dose escalation.
### DOSE MODIFICATIONS

**Haematological Toxicity**

<table>
<thead>
<tr>
<th>Neutrophil &amp; Platelet count x10⁹/L</th>
<th>Alemtuzumab Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils ≥ 0.25 and Platelets ≥ 25</td>
<td>Give 100%</td>
</tr>
<tr>
<td>Neutrophils &lt; 0.25 and Platelets &lt; 25</td>
<td>First occurrence: Hold treatment and restart at same dose when Neutrophils &gt; 0.5 x 10⁹/L and Platelets &gt; 50 x 10⁹/L (restart at 3mg if delay of ≥ 7 days)</td>
</tr>
<tr>
<td></td>
<td>Second occurrence: Hold treatment and restart at 3mg when Neutrophils &gt; 0.5 x 10⁹/L and Platelets &gt; 50 x 10⁹/L</td>
</tr>
<tr>
<td></td>
<td>Third occurrence: Permanently discontinue</td>
</tr>
</tbody>
</table>

If baseline Neutrophils < 0.5 X 10⁹/L and/or Platelets < 25 X 10⁹/L at initiation of therapy: If these blood counts decrease to <50% of baseline value, hold therapy and resume treatment when Neutrophils and Platelets return to baseline values. Restart at 3mg if delay ≥ 7 days.

Discontinue treatment permanently if autoimmune haemolytic anaemia or immune thrombocytopenia develops during treatment.

**Renal Impairment:** No dose adjustment required

**Hepatic Impairment:** No dose adjustment required

### CONTRAINDICATIONS

Alemtuzumab is contraindicated in patients with active systemic infections, underlying immunodeficiency (e.g. HIV), or known hypersensitivity or anaphylactic reactions to Alemtuzumab or one of its components.

Breast-feeding should be discontinued during treatment and for at least 3 months following the last dose of Alemtuzumab.

### PRECAUTIONS

**Infection**

Patients are at risk of Infections: Pneumocystis Pneumonia, adenovirus, invasive fungal infections, Cytomegalovirus and toxoplasma reactivation, Herpes Simplex Virus, Varicella Zoster Virus.

**Immunogenicity**

Patients who develop hypersensitivity to Alemtuzumab may have allergic or hypersensitivity reactions to other monoclonal antibodies.

**Carcinogenesis, Mutagenesis, Impairment of Fertility**

Women of childbearing potential and men of reproductive potential should use effective contraceptive methods during treatment and for a minimum of 6 months following Alemtuzumab therapy.
Pregnancy
Alemtuzumab may cross the placental barrier and cause fetal B and T lymphocyte depletion. Alemtuzumab should be given to a pregnant woman only if clearly needed.

Toxicities: Myelosuppression; infections; flu-like symptoms; hypotension; nausea; vomiting; diarrhoea; insomnia; allergic reactions

Drug interactions: Alemtuzumab
- Chemotherapeutic agents should be given 3 weeks apart
- Live viral vaccines should be given at least 12 months apart following Alemtuzumab therapy

References: www.medicines.org.uk
Bernego MG et al. Haematologica (2007);92: 784-794
Trautinger F et al. Eur J Cancer (2006); 42 (8):1014-1030
### Table 1 Objective Primary Disease Response Evaluation Criteria (OPDREC)

<table>
<thead>
<tr>
<th>Response Definition*</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients without Erythroderma</strong></td>
<td><strong>Patients with Erythroderma</strong></td>
</tr>
<tr>
<td><strong>Complete Response (CR)</strong></td>
<td>Complete resolution of skin patches, skin plaques and skin tumours</td>
</tr>
<tr>
<td></td>
<td>Absence of circulating Sézary cells</td>
</tr>
<tr>
<td></td>
<td>No evidence of abnormal lymph nodes and new tumour (cutaneous or non-cutaneous)</td>
</tr>
<tr>
<td></td>
<td><strong>PLUS</strong> Confirmation by skin biopsy.</td>
</tr>
<tr>
<td></td>
<td>Complete resolution of erythroderma</td>
</tr>
<tr>
<td></td>
<td>Absence of circulating Sézary cells</td>
</tr>
<tr>
<td></td>
<td>No evidence of abnormal lymph nodes and new tumour (cutaneous or non-cutaneous)</td>
</tr>
<tr>
<td></td>
<td><strong>PLUS</strong> confirmation by skin biopsy.</td>
</tr>
<tr>
<td><strong>Clinical Complete Response (CCR)</strong></td>
<td>Complete resolution of skin patches, skin plaques, and skin tumours</td>
</tr>
<tr>
<td></td>
<td>Absence of circulating Sézary cells</td>
</tr>
<tr>
<td></td>
<td>No evidence of abnormal lymph nodes and new tumour (cutaneous or non-cutaneous)</td>
</tr>
<tr>
<td><strong>Partial Response (PR)</strong></td>
<td>≥ 50% improvement in the summation of (\Delta) Skin + (\Delta) Lymph Node + (\Delta) Peripheral Blood with at least ≥ 30% improvement in (\Delta) Skin and no worsening in Lymph Node or Sézary cells</td>
</tr>
<tr>
<td></td>
<td>No evidence of new tumours (cutaneous or non-cutaneous)</td>
</tr>
<tr>
<td><strong>Stable Disease (SD)</strong></td>
<td>Patients who do not have enough improvement or worsening improvement in the summation of (\Delta) Skin + (\Delta) Lymph Node + (\Delta) Peripheral Blood to qualify as PR or PD, respectively</td>
</tr>
<tr>
<td></td>
<td>No evidence of new tumour (cutaneous or non-cutaneous).</td>
</tr>
<tr>
<td><strong>Progressive Disease (PD)</strong></td>
<td>Evidence of new tumour (cutaneous or non-cutaneous)</td>
</tr>
<tr>
<td></td>
<td>OR &gt; 25% worsening in the summation of (\Delta) Skin + (\Delta) Lymph Node + (\Delta) Peripheral Blood with &gt;15% worsening in (\Delta) Skin</td>
</tr>
</tbody>
</table>

* A confirmed assessment is one that is repeated at least 1 month after the initial assessment. To be classified as CR, CCR, or PR the response must be a confirmed assessment.

**Note:** If individual plaque radiation becomes necessary in an otherwise responding patient, the irradiated lesion will no longer be assessable for response. These patients will NOT be eligible for assessment as CCR or CR and shall be assessed as PR, assuming other criteria for this designation are met.

\(\Delta\) Skin (patients without erythroderma), = % change in the total score from baseline of the Weighted Body Surface Area Evaluation, (see Appendix 2).

\(\Delta\) Skin (patients with erythroderma), = % change in the total score from baseline based on the Erythroderma Scale, (see Appendix 2).

\(\Delta\) Lymph Node = % change in the size of abnormal lymph nodes (sum of longest diameter) from baseline based on physical examination and/or CT/MRI scan.

\(\Delta\) Peripheral Blood = % change in the absolute number of circulating Sézary cells from baseline.
Appendix 2:

ASSESSMENT OF SKIN DISEASE

Accurate measurement of disease burden and any changes resulting from treatment are an essential part of clinical trials. The standard methods for assessing response in Lymphoma are primarily based on measuring changes in the size of involved lymph nodes. These methods are inappropriate for evaluating disease burden in CTCL where most of the disease is in the skin.

A number of methods have been used for evaluating CTCL and these include:

1) Physicians Global Assessment (PGA) of disease on a 0-3 scale where
   - 0=no disease
   - 1=mild disease
   - 2=moderate disease
   - 3=severe disease

2) Percentage total body surface area (%TBSA) involved with disease to be evaluated, in adults, using the table below

<table>
<thead>
<tr>
<th>Anatomic structure</th>
<th>Surface area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head</td>
<td>9%</td>
</tr>
<tr>
<td>Anterior torso</td>
<td>18%</td>
</tr>
<tr>
<td>Posterior torso</td>
<td>18%</td>
</tr>
<tr>
<td>Each leg</td>
<td>18%</td>
</tr>
<tr>
<td>Each arm</td>
<td>9%</td>
</tr>
<tr>
<td>Genital/perineum</td>
<td>1%</td>
</tr>
</tbody>
</table>

Both of these methods have shortcomings - The PGA is a 4 point scoring system which provides little flexibility and sensitivity. % TBSA also lack sensitivity because it takes no account of the severity of the disease.

Therefore, the Severity-Weighted Assessment Tool (SWAT) has been proposed to evaluate Mycosis Fungoides type CTCL. The SWAT score represents the product of the %TBSA involvement of each lesion type multiplied by a weighting factor. The tumour types and their respective weighting factors are as follows:

- Patch 1
- Plaque 2
- Tumour or ulceration 3

This SWAT score can then be calculated according to the following formula

\[
\text{SWAT} = (\text{patch} \times \% \text{TBSA} \times 1) + (\text{plaque} \times \% \text{TBSA} \times 2) + (\text{tumour or ulcer} \times \% \text{TBSA} \times 3)
\]

Using this formula derives a score of 0 – 300 and by measuring SWAT at each visit it is possible to determine the percentage change from the baseline score and use this to measure response.
For patients with erythrodermic CTCL, a modified version of the SWAT will be used where the degree of oedema or infiltration will be used to map skin severity. The following weighting will be used:

- Erythroderma with mild infiltration mapped as patch disease x 1 erythema but no oedema or fissuring
- Erythroderma with moderate infiltration mapped as plaques x 2 erythema with oedema, or exudation
- Erythroderma with tumourous infiltration or ulceration (including fissuring) mapped as tumours or ulceration x 3 erythema with tumourous lesions or ulceration

The SWAT score for patients with erythrodermic CTCL can then be calculated using the following formula:

\[
\text{SWAT} = (\text{mild } \% \text{TBSA} \times 1) + (\text{moderate } \% \text{TBSA} \times 2) + (\text{tumourous or ulcerative } \% \text{TBSA} \times 3)
\]

References

Appendix 1