LONDON CANCER ALLIANCE West and South

Skin Pathway Group – Alemtuzumab in Cutaneous Lymphoma

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

Alemtuzumab is not licensed for this indication, and therefore use should be in line with indicidual Trust governance process

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:

Week 1	Alemtuzumab SC	3mg	Day 1
	Alemtuzumab SC	10mg	Day 3 and Day 5
Thereafter	Alemtuzumab SC	10mg	Three times a week (usually Monday, Wednesday and Friday)

If Alemtuzumab is interrupted for ≥ 7 days, restart at 3mg

Administration: Subcutaneous (Unlicensed use)

Version: 1.0 Supersedes: all other versions	Approved by LCA Skin Pathway Chemotherapy Lead: Mark Harries
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Ravi Shaunak	Approved by LCA Medicines & Chemotherapy Steering Group Chair:
Second check by: Sanna Eestila	Date prepared: January 2015 Review Date: January 2017

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.

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

Frequency:

Continued for up to 12 weeks
Discontinue treatment if:

- Complete Clinical Response (CCR)
- Progressive Disease (PD)
- No further improvement between 4 and 8 week assessment
- Neutrophils < 0.25 x 10^6/L, platelets < 25 x 10^6/L (see Haematological toxicity)

Patients who have CCR can be re-treated on relapse

Pre-medication:

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

Anti- emetics:

Low emetogenicity
Follow Local Anti-emetic Policy

Supportive medication:

<u>Prophylaxis</u> (During and to continue for 2 months after Alemtuzumab or until CD4 > 200)
Co-trimoxazole dose as per local policy
Aciclovir as per local policy
Antifungal prophylaxis as per local policy
Allopurinol 300mg OD orally (100mg if renal impairment, CrCl < 20ml/min)

When neutrophils < 0.5 x 10^9/L
Ciprofloxacin 500mg BD

Growth Factor support should be considered in neutropenic patients

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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

Pre-treatment Investigations:

- FBC, 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 investigations:

FBC	Prior to each dose
Lymphocyte subsets	Weekly
LFTs	Weekly
U&Es	Weekly
Glucose	Weekly
PCR for CMV viral load in CMV positive patients	Weekly (see CMV Monitoring)
Clinical review (skin, lymph nodes, side effects)	Every 2 weeks
CT scan	Every 4 weeks

Sezary Count	After 4th dose and then at 4 weeks, 8 weeks and 12 weeks
<u>CMV Monitoring:</u>	Baseline PCR for CMV Weekly PCR for CMV IgG in CMV positive patients

In the presence of CMV reactivation:
Discontinue Alemtuzumab
Start Gangciclovir or valganciclovir as per local practice
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 Valgancyclovir 900mg bd for 14-21 days. Consultant decision only

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

<u>After discontinuation of Alemtuzumab</u>, monitor:

U&E/Cr	Every 2 weeks in the first month and then Monthly
CMV viral load in CMV positive patients	Monthly, for 6 months
Thyroid Function	Monthly
Sezary Counts	Monthly

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

DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		**Platelets (x 10^9/L)**	**Dose**
≥ 0.25	**&**	≥ 25	Give 100%
< 0.25	**&**	< 25	First occurrence: Hold treatment and restart at same dose when Neutrophils > 0.5 x 10^9/L and Platelets > 50 x 10^9/L (restart at 3mg if delay of ≥ 7 days)

			Second occurrence: Hold treatment and restart at 3mg when Neutrophils > 0.5 x 10^9/L and Platelets > 50 x 10^9/L
			Third occurrence: Permanently discontinue

If baseline Neutrophils < 0.5 X 10^9/L and/or Platelets < 25 X 10^9/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

Non-haematological Toxicities

Renal Impairment No dose adjustment required

Hepatic Impairment No dose adjustment required

Location of regimen delivery: Day-case setting

Comments: Alemtuzumab 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) 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 reinstituted with gradual dose escalation

Drug interactions: Live viral vaccines should be given at least 12 months apart following Alemtuzumab therapy

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

References:

www.medicines.org.uk
Bernego MG et al. Haematologica (2007);92: 784-794
Lundin J et al. Blood, 1 June 2003. 101 (11): 4267-4272
Lundin J et al. Blood, 15 May 2005. 105 (10): 4148-4149
Trautinger F et al. Eur J Cancer (2006); 42 (8):1014-1030
Whittaker SJ et al. Br J Dermatol. 2003; 149 (6): 1095-1107