PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Alemtuzumab (Campath®) & IV Cladribine (Leustat) T-Cell Prolymphocytic Leukaemia (TPLL)

PROTOCOL REF: MPHAACCL
(Version No. 1.0)

Approved for use in:

Alemtuzumab (Campath®)

- First-line or Relapsed T-cell prolymphocytic leukaemia (TPLL)

Alemtuzumab (Campath®) is not licensed in the United Kingdom but is available through the Clinigen Alemtuzumab Patient Access Scheme on an individual patient basis.

Blueteq registration is not required

Requires approval and ordering of stock via Clinigen Patient Access Scheme

Dosage: Week 1

Drug	Dose	Route	Frequency
Alemtuzumab (Campath®)	**3mg**	IV infusion	Day 1
Alemtuzumab (Campath®)	**10mg**	IV Infusion	Day 3
Alemtuzumab (Campath®)	**30mg**	IV Infusion	Day 5

Dosage: Weeks 2 to 3

Drug	Dose	Route	Frequency
Alemtuzumab (Campath®)	**30mg**	IV infusion	Day 1, 3 and 5 (Monday, Wednesday & Friday)

Cladribine (Leustat)

Consider the addition of cladribine as an option in adults with T-Cell Prolymphocytic Leukaemia where the use of pentostatin is either inappropriate or unavailable. And only if there has been an inadequate response to alemtuzumab monotherapy after 3 weeks of treatment. This is typically, where there is a high tumour bulk and WBC remains elevated after initiating treatment. If responding well, continue on alemtuzumab monotherapy.

Cladribine (Leustat) is unlicensed for T-PLL.

Dosage: Weeks 4 to 16

Drug	Dose	Route	Frequency
Alemtuzumab (Campath®)	**30mg**	IV infusion	Day 1, 3 and 5 of each week (option to increase frequency to x5/week)
Add cladribine below if inadequate response to alemtuzumab monotherapy			
Cladribine (Leustat)	**5mg/m^2**	IV Infusion	Day 1,2,3,4 and 5 of weeks 4,8,12,16

Dosage: Weeks 20 and 24

Drug	Dose	Route	Frequency
Cladribine (Leustat)	**5 mg/m^2**	IV infusion	Days 1-5 only of weeks 20 and 24

Alemtuzumab (Campath®)

Minimum 4 weeks, maximum 16 weeks of treatment.

Cladribine (Leustat)

Maximum of 6 cycles.

Response to cladribine therapy should be determined and evaluated every two cycles of treatment. If no clinical benefit has been seen, treatment should be stopped.

Administration & Counselling points:

Alemtuzumab (Campath®

- Patients must receive irradiated bloods products indefinitely once treatment has started
- Patients must be monitored weekly for CMV reactivation
- If treatment is delayed for more than 7 days for any reason, alemtuzumab should be reinstituted with the dose escalation from 3 mg.
- If acute moderate to severe adverse reactions due to cytokine release (hypotension, rigors, fever, shortness of breath, chills, rashes and bronchospasm) occur at either the 3 mg or 10 mg dose levels, then those doses should be repeated daily until they are well tolerated before further dose escalation is attempted.

Cladribine (Leustat)

Patients will require irradiated blood products (lifelong) – the patients receive information booklets about irradiated blood when counselled by specialist nurses. It contains an alert card that the patient then carries around with them. The specialist nurses will contact the lab to inform them of the need for irradiated blood products.

Emetogenic risk:

Alemtuzumab (Campath®): Mildly emetogenic.
Cladribine (Leustat): Mildly emetogenic

Supportive treatments:

Pre-infusion medications to be given at least 30 minutes before Alemtuzumab (Campath®):

- Hydrocortisone 100mg IV
- Chlorphenamine 10mg IV
- Paracetamol 1g oral

(Required before the first dose and with each dose escalation, thereafter as clinically indicated).

Other supportive medications:

- Allopurinol 300mg PO once daily for duration of first cycle (then review)
- Aciclovir 400mg PO twice daily during and up to 3 months after the completion of treatment
- Posaconazole PO 300mg BD for one day then 300mg OD
- Metoclopramide PO 10mg TDS PRN
- Co-trimoxazole 480mg PO once daily during and up to 3 months after the completion of treatment

Extravasation risk:

Alemtuzumab (Campath®): Non-vesicant
Cladribine: Non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries

Interactions:

Alemtuzumab (Campath®):

No formal drug studies have been conducted

Cladribine (Leustat)

Cladribine (Leustat) is recommended not be used concomitantly with other nucleoside analogues such as fludarabine or live attenuated vaccinations

Cladribine (Leustat) interacts with medicines undergoing intracellular phosphorylation or with inhibitors of adenosine uptake such as didanosine, tenofovir, adefovir.

Please consult summary of product characteristics via https://www.medicines.org.uk/emc for full list of interactions.

Treatment schedule:

Treatment schedule week 1:

Day	Drug	Dose	Route	Diluent and rate
1	**Hydrocortisone sodium succinate**	100mg	IV bolus	Over 3-5 minutes
	Paracetamol	1g	PO	
	Chlorphenamine	10mg	IV bolus	Over 3-5 minutes
	Alemtuzumab (Campath®)	3mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours
3	**Hydrocortisone sodium succinate**	100mg	IV bolus	Over 3-5 minutes
	Paracetamol	1g	PO	
	Chlorphenamine	10mg	IV bolus	Over 3-5 minutes
	Alemtuzumab (Campath®)	10mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours
5	**Hydrocortisone sodium succinate**	100mg	IV bolus	Over 3-5 minutes
	Paracetamol	1g	PO	
	Chlorphenamine	10mg	IV bolus	Over 3-5 minutes
	Alemtuzumab (Campath®)	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours

Treatment schedule weeks 2 and 3:

Continue as below up to week 16 if continuing with alemtuzumab monotherapy and alemtuzumab well tolerated:

Day	Drug	Dose	Route	Diluent and rate
1	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours
3	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours
5	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours

If cladribine therapy added, proceed as below:

Treatment schedule weeks 4 to 15 (4 week cycles):

Day	Drug	Dose	Route	Diluent and rate
1	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
	Alemtuzumab (Campath®)	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
2	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
3	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
	Alemtuzumab (Campath®)	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
4	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
5	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
	Alemtuzumab (Campath®)	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
8	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
10	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*

12	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
15	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
17	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
19	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
22	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
24	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
26	**Alemtuzumab (Campath®)**	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*

*If patient has been tolerating alemtuzumab (Campath®) with no signs of infusion related reaction(s), the rate of infusion can be increased. Can be given over 2 hours at discretion of the prescribing Consultant. NB this is on off-label use of alemtuzumab and patient consent is needed.

Treatment schedule week 16

Day	Drug	Dose	Route	Diluent and rate
1	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 250mL sodium Chloride 0.9% over 2 hours
	Alemtuzumab (Campath®)	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
2	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
3	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
	Alemtuzumab (Campath®)	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*
4	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
5	**Cladribine (Leustat)**	5 mg/m^2	IV infusion	In 100mL sodium Chloride 0.9% over 2 hours
	Alemtuzumab (Campath®)	30mg	IV infusion	In 100ml Sodium Chloride 0.9% over 4 hours*

Treatment schedule weeks 20 and 24 (4 week cycles)

Day	Drug	Dose	Route	Diluent and rate
1	**Cladribine (Leustat)**	5 mg/m^2	IV	In 100mL sodium Chloride 0.9% over 2 hours
2	**Cladribine (Leustat)**	5 mg/m^2	IV	In 100mL sodium Chloride 0.9% over 2 hours
3	**Cladribine (Leustat)**	5 mg/m^2	IV	In 100mL sodium Chloride 0.9% over 2 hours
4	**Cladribine (Leustat)**	5 mg/m^2	IV	In 100mL sodium Chloride 0.9% over 2 hours
5	**Cladribine (Leustat)**	5 mg/m^2	IV	In 100mL sodium Chloride 0.9% over 2 hours

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea

Alemtuzumab (Campath®)
Rigors develop during the first few injections. Infusion-related fever more common during the first week and commonly begins 5 - 6 hours after the infusion starts. Hypotension, dyspnoea, rashes, headache and diarrhoea. Thrombocytopenia most common during weeks 24 and neutropenia common between weeks 4 - 8.
Cladribine (Leustat)
Infection, fever, skin rashes, lethargy, anorexia, headache. Note: Risk of secondary malignancy

Investigations and treatment plan:

	Pre	Week 1	Week 2-3	Week 4	Week 5-7	Week 8	Week 9-11	Week 12	Week 13-15	Week 16	Week 20	Week 24	Ongoing
Informed Consent	X												
Clinical Assessment	X	X	X	X	X	X	X	X	X	X	X	X	Every week
SACT Assessment (to include PS and toxicities)		X	X	X	X	X	X	X	X	X	X	X	Every week
On treatment review				X		X		X		X	X	X	
FBC	X	X	X	X	X	X	X	X	X	X	X	X	Every week (Can move to fortnightly if stable)
U&E & LFTs & Calcium profile	X	X	X	X	X	X	X	X	X	X	X	X	Every week
CrCl (Weight formula)	X	X	X	X	X	X	X	X	X	X	X	X	Every week
CT scan/bone marrow biopsy	X												Repeat at the end of treatment
ECG/ECHO	X												If clinically indicated
CMV PCR monitoring	X	X	X	X	X	X	X	X	X	X	X	X	Weekly for duration of treatment and after at discretion of prescriber
Blood pressure	X	X	X	X	X	X	X	X	X	X	X	X	Continuous monitoring required if on Alemtuzumab
Temperature, respiratory rate, pulse	X	X	X	X	X	X	X	X	X	X	X	X	Continuous monitoring required if on Alemtuzumab
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X												If clinically indicated

Viral swabs (including COVID-19)	X												
Weight recorded	X				X		X		X		X	X	Every week
Height recorded	X				X		X		X		X	X	Every week
Serum Pregnancy test	X												Where appropriate
Fertility counselling	X												Where appropriate

Dose Modifications and Toxicity Management:

Haematological toxicity:

No reductions required prior to starting treatment.

Alemtuzumab (Campath®):

	Blood Parameter	Dose Modification
1st Occurrence	ANC <0.2 x10^9/L or Platelet ≤ 25 x 10^9/L	Withhold alemtuzumab until recovery of ANC >0.5 x10^9/L and platelet > 50 x 10^9/L. Resume at same dose (i.e. 30mg). Consider GCSF support.
2nd Occurrence	ANC <0.2 x10^9/L or Platelet ≤ 25 x 10^9/L	Withhold alemtuzumab until recovery of ANC >0.5 x10^9/L and platelet > 50 x 10^9/L. Resume at reduced dose (i.e. 10mg). Consider GCSF support.
3rd Occurrence	ANC <0.2 x10^9/L or Platelet ≤ 25 x 10^9/L	Discontinue alemtuzumab
If there is a ≥ 50% decrease from baseline value in patients initiating therapy with a baseline ANC <0.2 x10^9/L or platelet ≤ 25 x 10^9/L then follow the above steps (i.e. 1st occurrence withhold until recover to baseline and resume at current dose, 2nd occurrence resume at reduced dose of 10mg, 3rd occurrence discontinue)		

Cladribine (Leustat):

If ANC < 1.0 x 10^9/L and platelets <100 x 10^9/L contact the consultant haematologist for advice.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity

Dosing in renal and hepatic impairment:

Alemtuzumab (Campath®)

Renal and Hepatic
Alemtuzumab has not been studied in patients with renal or hepatic impairment

Cladribine (Leustat)

Renal	
Limited experience in patients with impaired renal function	
CrCl (mL/min)	Advice
≤ 50	Not recommended
Hepatic	
Due to limited experience treating patients with abnormal liver function, treatment should be approached with caution.	
Child-Pugh Score	Advice
A	No need for dose adjustment
B or C	Not recommended

Management of infusion related toxicities with alemtuzumab:

- Hydrocortisone 50-100 mg IV may be given pre-treatment in the event of continued infusion related toxicity.
- If rigors develop, halt infusion and administer IV chlorphenamine.

- In patients experiencing rash, an additional 4 mg chlorphenamine PO every 4 - 6 hours as needed is indicated. In patients experiencing severe rash, pre-medication with H2 receptor antagonist (e.g. famotidine) is recommended.
- Treating physicians are advised to use antibiotics and G-CSF support according to their clinical judgment for febrile neutropenia
- If hypotension develops, hydration with normal saline is indicated, unless contraindicated based on underlying cardiac status
- If dyspnoea develops, infusion should be stopped and treatment with inhaled beta2 agonists should be administered if needed - severe dyspnoea may require the temporary use of steroids.

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Circulation/Dissemination

Date added into Q-Pulse	2nd February 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
October 2022	1.0	**Thomas Sanders, Pharmacist**	New document