Cyclophosphamide/TBI/Alemtuzumab for MUD Transplant

Summary of Schedule

Date:

	Day													
DRUG	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**+1**	**+3**	**+6**	**+11**
Admission	*													
Alemtuzumab (Campath) *Antibody to suppress immune system*		*	*											
Methylprednisolone *To minimise reactions to Campath*		**	*											
Cyclophosphamide *Chemotherapy*				*	*									
Mesna *To protect your bladder from Cyclophosphamide*				****	****									
TBI - *Total Body Irradiation* *to destroy bone marrow*						Dose 1&2	Dose 3&4	Dose 5&6	Dose 7&8					
Bone marrow/stem cell infusion										*				
Pentamidine *Prevents a specific pneumonia called PCP*											*			
Methotrexate Days +1,+3,+6,(+11) *Continues to suppress immune system*											*	*	*	(*) Not always given
Ciclosporin *Continues to suppress immune system*							**	**	**	**	**	**	**	**
Ondansetron (O) Dexamethasone (D) Metoclopramide (M) *Different types of anti-sickness*				O D M	O D M	O D M	O D M	O D M	O D M	O M				

Indications
Acute myeloid leukaemia
Chronic myeloid leukaemia
Acute lymphoblastic leukaemia

Pre-assessment

- Ensure pre-transplant investigations are carried out as per Checklist/Record B3.10b
- Ensure patient has a suitable central line in situ
- Ensure results of pre-transplant investigations are checked by a Haematology SpR and recorded on Checklist/Record B.3.10b
- Ensure patient consent has been obtained
- Haematology SpR to complete electronic BMT front sheet and email to the Administrator to the BMT Nurses to distribute
- Prescribe chemotherapy and supportive treatment at least 5 days before admission
- Send NHSBT referral form at least one working day before the start of patient conditioning
- Ensure donor clearance is obtained and reviewed by a BMT consultant prior to patient admission
- Ensure that patient receives irradiated blood products from the start of conditioning and indefinitely thereafter
- Ensure pregnancy test is carried out immediately before commencing conditioning treatment, on all women of child-bearing potential unless they have been sterilized or have undergone a hysterectomy
- Treatment should be agreed in the relevant MDT and regimen documented on the MDT proforma
- **Ambulatory delivery:** Ensure the patients meets the criteria in line with the Ambulatory Care Operational Policy

Chemotherapy and fluids
Encourage 3L oral fluids daily, give iv if oral intake insufficient.

Day -8		
08.30	**Pre-medication** (30-60 minutes prior to Alemtuzumab	**Methylprednisolone sodium succinate 1mg/kg** in 100ml sodium chloride 0.9% iv infusion over 15 minutes. Chlorphenamine 10mg iv. Paracetamol 1g PO
0900	**Alemtuzumab**	**30mg od** in 500ml sodium chloride 0.9% iv infusion. The rate should be increased incrementally as follows: 1mg/hour for 1 hour = 17ml/hr 2mg/hour for 1 hour = 34ml/hr 3mg/hour for 1hour = 50ml/hr 4mg/hour for 1 hour = 67ml/hr 5mg/hour for 1 hour = 84ml/hr 6mg/hour for rest of infusion = 100ml/hour
18.00	**Post-medication**	**Methylprednisolone sodium succinate 1mg/kg** in 100ml sodium chloride 0.9% iv infusion over 15 minutes.

Day –7 *08:30*	**Pre-medication**	**Methylprednisolone sodium succinate 1mg/kg** in 100ml sodium chloride 0.9% iv infusion over 15 minutes. Chlorphenamine 10mg iv. Paracetamol 1g PO
09.00	**Alemtuzumab**	**30mg od** in 500ml sodium chloride 0.9%, iv infusion. If the patient tolerated the previous infusion, the infusion rate should be started and increased incrementally as follows: 3mg/hour for 1 hour = 50ml/hr 4mg/hour for 1 hour = 67ml/hr 5mg/hour for 1 hour = 84ml/hr 6mg/hour for rest of infusion = 100ml/hour In the event of a previous reaction, give as per day –8
Day –6 to -5 *00.00*	**Pre-hydration**	1000ml sodium chloride 0.9% iv infusion over 8hrs
08.00	**Pre-hydration**	500ml glucose 5% iv infusion over 2hrs Furosemide 20mg iv, then prn to maintain urine output >100ml/hr
10.00 (T=0)	**Cyclophosphamide**	**60mg/kg od** in 500ml sodium chloride 0.9% iv infusion over 1hr
T=0, 3, 6, & 9 *hours*	**Mesna**	**24mg/kg** in 100ml sodium chloride 0.9% iv infusion over 15 minutes
11.00 (T = 1)	**Post-hydration**	1000ml sodium chloride 0.9% iv infusion over 6hrs
17.00 (T = 7)	**Post-hydration**	1000ml sodium chloride 0.9% iv infusion over 6hr
Day –4 to -1	**TBI**	One TBI fraction in morning and one in afternoon. Check exact time with radiotherapy dept.
Day 0 *10.00*	**Pre-hydration**	500ml sodium chloride 0.9% iv infusion over 2hrs
	Marrow/stem cell infusion (min. 48hrs post cyclo)	give hydrocortisone 100mg iv and chlorphenamine 10mg iv 15 minutes before cell infusion
Day +1	**Pentamidine**	**4mg/kg** (max 300mg) in 100ml sodium chloride 0.9% iv infusion over 1 hour
	Methotrexate	**15mg/m^2 iv bolus** (min. 24hr post cell infusion)

Day +3,+6 (+11) *At the same time as Day 1*	**Methotrexate**	**10mg/m^2 iv bolus** (day +11, check with consultant).

Dose modification
Cyclophosphamide and Methotrexate - Consider dose reduction if renal function is impaired, discuss with consultant.

Antiemetics

Day –6 to 0	Ondansetron 8mg po/iv/bd Metoclopramide 20mg po/iv/qds
Day –6 to –5	Dexamethasone 8mg po/iv/od
Day -4 to -1	Dexamethasone 8mg po/iv/bd (0700 and 1300)

Extravasation
Cyclophosphamide- neutral
Alemtuzumab- Neutral

Concurrent medication

Avoidance of Penicillin during period of Post-transplant Methotrexate: To prevent inadvertent concurrent prescribing of penicillin during post-cell methotrexate administration period, annotate the patient's electronic prescribing record (under allergies→Type= toxicity→comments) with the following warning "avoid penicillin from Day 0 to Day +14 of transplant due to interaction with post-cell methotrexate leading to increased methotrexate blood levels and associated risk of methotrexate toxicity. Use of Meropenem is permitted during this period".

Ciclosporin Day -3	Start orally on Day -3. Refer to protocol NSSG>BMT>GvHD> B.2.19 Ciclosporin		
Antifungal prophylaxis	Refer to Protocol NSSG>BMT>Clinical Management> H.94 Antifungal Therapy Guidelines Start from day 0 until neutrophils >0.5x10^9/L (or longer if on steroids). If clinically appropriate discontinue antifungals a few days prior to discharge to enable appropriate dose adjustments of immunosuppression.		
CMV, HSV and VZV prophylaxis Note: Letermovir requires **BLUTEQ form**	**Recipient CMV status**	**Donor CMV status**	**Antiviral Prophylaxis**
	Seropositive (+)	Seropositive (+)	Letermovir 480mg OD (**240mg OD** in patients taking ciclosporin) PO/IV from day 0 to day +100 **PLUS** aciclovir 200mg PO TDS from start of conditioning until 24 months post-transplant.
	Seropositive (+)	Seronegative (-)	Letermovir 480mg OD (**240mg OD** in patients taking ciclosporin) PO/IV from day 0 to day +100 **PLUS** aciclovir 200mg PO TDS from start of conditioning until 24 months post-transplant.
	Seronegative (-)	Seropositive (+)	Aciclovir 500mg/m^2 IV TDS or 800mg PO QDS from start of conditioning till day +30 then 800mg PO QDS

			for 3 months, then 200mg TDS until 24 months post-transplant
	Seronegative (-)	Seronegative (-)	Aciclovir 250mg/m^2 IV TDS or 200mg PO TDS form start of conditioning until 24 months post-transplant
Pentamidine Day +1	4mg/kg/day (max 300mg) iv on day+1 and day +30 (unless started on co-trimoxazole).		
Omeprazole	20mg OD from start of conditioning until platelet count >50x10^9/L		
Norethisterone	5-10mg po TDS from day 0 until platelets >50x10^9/L (menstruating women only)		
Ursodeoxycolic acid	Refer to protocol: NSSG>BMT>Clinical Management> B.2.12 VOD		
Allopurinol	300mg po od for 7 days from Day -8. Only in patients with acute leukaemia who are not in remission		

Investigations

Daily	FBC, creatinine, urea & electrolytes, weight
Alternate days	liver function tests
Mon/Thurs	clotting, calcium, magnesium, phosphate
Mon/Fri	group and save
Monday	Ciclosporin levels - trough level. See protocol. CMV PCR from Day+1 EBV PCR weekly from Day +1
Other	Other specimens for virology as clinically indicated. Chest X-ray weekly and as clinically indicated

Medication on discharge (TTO's)

Ciclosporin	Refer to protocol NSSG>BMT>GvHD> B.2.19 Ciclosporin
Antifungal Prophylaxis	Refer to Protocol NSSG>BMT>Clinical Management> H.94 Antifungal Therapy Guidelines Stop when neutrophils >0.5x 10^9/l (orlonger if on steroids). If clinically appropriate discontinue antifungals a few days prior to discharge to enable appropriate dose adjustments of immunosuppression
Aciclovir	Refer to concurrent medications in this protocol
Letermovir	Refer to concurrent medications in this protocol
Co-trimoxazole	480mg po daily Mon, Wed, Fri: start when neutrophils >1x10^9/l and continue until one month after immunosuppressive therapy stopped and CD4 count ≥ 0.2 x 10^9/L. Then increase to 960mg when counts stable. If allergic to co-trimoxazole, Pentamidine 4mg/kg (max dose 300mg) iv monthly
Penicillin V	250mg BD for life. Erythromycin for penicillin allergic
Omeprazole	Stop when platelets >50 x 10^9/l unless clinically indicated
Norethisterone	Stop when platelets >50 x 10^9/l

References

1. Mackinnon S, Milligan D, Craddock C, Chopra R, Hale G. Phase II study of low intensity

allogeneic stem cell transplantation using a conditioning regimen containing Fludarabine and Melphalan. Effect of Campath-1H dose reduction on the incidence of graft versus host disease and infectious complications. Sept 2001
2. University College Hospital, London: Allogeneic Transplant Policy, author Dr Stephen Mackinnon MD
3. Genzyme Corp. CAMPATH (alemtuzumab) Summary of Product Characteristics. 2014.
4. Cullis JO et al. Matched unrelated donor bone marrow transplantation for chronic myeloid leukaemia in chronic phase: comparison of ex vivo and in vivo T-cell depletion. Bone Marrow Transplant. 1993;11 Suppl 1: 107-11
5. Goldspiel J et al. Stability of alemtuzumab solutions at room temperature. Am J Health-syst Pharm . 2013; 70:439-442

Author(s) Clinical Protocol:
Tim Littlewood, BMT Programme Director, Version 5, 2008
Marc Mitchell, Divisional Pharmacist Version 5, 2008
Denise Wareham BMT Coordinator, Amendments 2009

Authorised by: Dr Andy Peniket, BMT Lead

Review

Name	Revision	Date	Version	Review date
Dr Andy Peniket, BMT Director	TBI BD fractionation	Sept 2011	7.0	Sept 2013
Dr Rob Danby, BMT Fellow Sandy Hayes, Quality Manager	Full review Reformat, oral ciclosporin, dalteparin	Oct 2014	8.0	October 2016
Sandy Hayes, Quality Manager	Addition of URSO	Nov 2014	8.1	Nov 2016
Cheuk-Kie Cheung, Specialist Cancer Pharmacist Denise Wareham, BMT Nurse Coordinator	Heparin, deltaparin alemtuzumab, anti-fungals, pentamidine Patient-friendly Summary of Schedule, generic changes	Feb 2017	9.0	Feb 2019
Dr Rob Danby, BMT consultant. Nadjoua Maouche, Lead Haematology Pharmacist	Protocol review day. Inclusion of campath pre-medication. Campath infusion rates. Anti-viral prophylaxis. Extravasation risk. Formatting	July 2019	9.1	July 2021
Denise Wareham, BMT Coordinator	Addition of nursing care plan as an integrated part of the document	Mar 2020	9.2	July 2021
Dr Robert Danby, Consultant Nadjoua Maouche, Lead Haematology Pharmacist	Protocol Review Day. Stopping criteria for septrin,and antifungals.	Apr 2023	9.3	Apr 2025

Denise Wareham, BMT Senior Specialist Nurse	Aciclovir duration. methotrexate and penicillin alert Amended pre-assessment generic information			

Nursing Care Plan on Next Page

Nursing Care Plan

Alemtuzumab (Campath) is a monoclonal antibody targeted against T lymphocytes. It is used to induce immunosuppression and reduce the risk of Graft versus Host Disease (GvHD).
Infusion-related side effects: fevers, chills, nausea, vomiting, allergic reaction, rash, pruritus, angioedema, bronchospasm and dyspnea, cytokine release syndrome.

Day -8 to -7

- Administer pre-medications as prescribed
- Commence Alemtuzumab as early as possible, i.e. before 10.00 am, so that the haematology medical team are available if reactions occur

If the patient develops signs of bronchospasm:

- Stop the infusion
- Administer Ventolin nebulisers as prescribed
- Monitor respiratory rate and oxygen saturation
- When symptoms have subsided restart infusion at same rate, or as directed by the clinician
- If symptoms persist seek medical advice
-

If the patient develops signs of allergic reaction:

- Stop the infusion
- Monitor vital signs including oxygen saturation
- Seek medical advice
- Administer Chlorphenamine or other medications as directed by clinician
- When symptoms have subsided restart infusion at same rate, or as directed by the clinician
- If symptoms persist seek medical advice.

Ambulatory and ward-based patients must have observations 6 hours after FIRST administration of Alemtuzumab

Cyclophosphamide is given to destroy abnormal cells and also to stop the patient's immune system from rejecting the donor stem cells.
Side effects: haemorrhagic cystitis, nausea and vomiting, dizziness, alopecia, mucositis and bone marrow ablation.

Day -6 to -5

- Commence IV fluid regime at midnight
- Administer pre-medications: anti emetics and Furosemide 30 mins before Cyclophosphamide
- **10.00** infuse Cyclophosphamide and Mesna over 1 hour
- Administer subsequent Mesna at **3, 6 and 9 hours** after Cyclophosphamide
- Ensure patient passes >100ml of urine hourly for 6 hours after the Cyclophosphamide. Test all urine for blood and report any haematuria to medical staff.
- Weigh twice daily and report weight gain or positive fluid balance > 2L
- Administer PRN Furosemide as clinically indicated

Total Body Irradiation (TBI) is given in combination with chemotherapy to destroy abnormal cells and also to stop the patient's immune system from rejecting the donor stem cells.
Side effects: nausea and vomiting, diarrhoea, mucositis, skin damage, veno-occlusive disease,

pneumonitis and bone marrow ablation

Day -4 to –1 (two fractions each day)

- Give prescribed anti-emetics prior to am and pm fraction
- Ensure patient is ready to go to radiotherapy by 08.00 and 16.00 unless otherwise instructed by the Radiotherapy Team. Assess the need for patient to be escorted or not

Ciclosporin is given as part of the immunosuppression regime

Day -3

- Commence orally, see protocol re management and levels, ensure a dedicated lumen of central line is used for levels when infusion is required

Stem Cell Infusion of fresh cells If stem cells are frozen and/or source is cord cells or bone marrow refer to alternative care plans located on NSSG > BMT > Nursing Care Plans
Potential complications: allergic reaction, fluid overload, infusion of micro-aggregates, pulmonary oedema, nausea, vomiting, diarrhoea, abdominal pain. Transfusion reaction in case of ABO mismatch.

Day 0

- Monitor patient closely and observe for any signs of reaction, fluid overload and/or respiratory compromise
- Positively identify the patient and donor ID on NHSBT Form 5071and bag(s)
- Check cells to ensure no clumping, or bag damage
- Take great care when spiking each bag, to prevent inappropriate puncturing. See Cell Management policy NSSG>BMT>Clinical Management, if bag is accidentally punctured
- Infuse cells over 30-40 mins per bag, depending on volume. The cells should ideally be infused through a:
  Central line using an appropriate infusion pump and correct giving set with a blood administration filter, side-armed with Sodium Chloride 0.9%
  OR, if the central line is not patent or has been removed
  Peripheral cannula, ideally pink 20G, in ACF if possible, using a blood administration giving set side-armed with Sodium Chloride 0.9% using a Y connector, and gravity feed
- Record lot numbers of giving sets and saline in medical notes
- Document volume of cells and cell count in the medical notes
- On completion of cells, continue flushing the IV line with saline until it runs clear
- Ensure a copy of the NHSBT form ‘Record of issue and infusion’ is filed in patient notes.
- Ensure completion of NHSBT adverse event form is completed and returned to Haematology Ward Clerk who will forward to NHSBT/SCI

Pentamidine isethionate is an antimicrobial medication primarily given for prevention and treatment of Pneumocystis pneumonia (PCP), a severe interstitial pneumonia often seen in patients that are immunocompromised.
Side Effects: can cause hypotension and arrhythmias if electrolytes have not been corrected

Day +1

- Bloods pre administration; U& E's, creatinine, and FBC
- Administer any replacements necessary prior to infusion
  Refer to guidelines for management of hypomagnesaemia in adult clinical haematology on NSSG>Clinical Haematology OUH>Haematology Day Treatment Unit
- Perform ECG pre, during and immediately after first dose. Check with the SHO or Registrar to ensure they are happy for you to commence infusion
- Check blood sugar is within normal range
- Check observations 30 minutes into infusion and 5 minutes after completion of infusion. (This only needs to be done on the first dose)
- Ensure the patient is lying down or sitting in a chair whilst the Pentamidine is being infused
- Wear gloves, and apron whilst hanging the bag
- Follow the above steps i.e. ECG's and observations
- Check blood sugar 60 minutes post infusion

NB. If the patient has experienced a previous reaction, you may need to consider slowing subsequent infusions. The patient may also require a pre-med of Paracetamol or anti-emetic. In these cases you may advice the patient to eat or drink something sweet during the infusion.

Methotrexate is an antimotabolite chemotherapy but used in this setting as part of the immunosuppression regime to reduce the risk of GvHD.
Side effects: with this small dose the main side effect is oral mucositis

Day +1, +3, +6 and (+11)

- Give the first dose, day +1, a minimum of 24 hours after the completion of stem cell/bone marrow infusion
- Day + 1, +3 and +6 are routinely given but please check with the medical team before giving day +11 as this dose may be omitted if the patient has severe oral mucositis

Author(s) Nursing Care Plan: Denise Wareham, BMT Coordinator

Authorised by: Rachel Miller, Deputy Matron

Circulation: NSSG Haematology Website, patient EPR

Audit: These processes are subject to OxBMT/IEC audit programme

Review

	Revision	Date	Version	Review date
Denise Wareham, BMT Coordinator	Revised nursing care plan and added as an integrated part of the clinical protocol	Mar 2020	1.0	July 2021 Align with clinical protocol
Denise Wareham, BMT Senior Specialist Nurse	Amendment to cell infusion	Apr 2022	1.1	Align with clinical protocol