Fludarabine/Melphalan/Alemtuzumab-RIC-SIB

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Reduced intensity conditioning for sibling donor allogeneic stem cell transplant in patients with lymphoproliferative disorders	C91	00611a	Hospital

TREATMENT:

Conditioning chemotherapy is administered over **7 days**. Stem cells are infused on **day 0**.

Facilities to treat anaphylaxis must be present when conditioning therapy and stem cells are administered.

Day	Drug	Dose	Route	Diluent & Rate
-7,-6,-5,-4-3	Fludarabine[a]	30mg/m^2	IV infusion	100mls sodium chloride 0.9% over 30 minutes
-2	Melphalan[b]	140mg/ m^2	IV push	Give as an IV push over 15-30 minutes via side-arm of a fast flowing sodium chloride 0.9% infusion
-1	Alemtuzumab	30mg	IV infusion	100mls sodium chloride 0.9% over 6 hours
0	Stem cell infusion			
Start +6 (until ANC > 1.0X10^9/L for two consecutive days)	Filgrastim (G-CSF)	5mcg/kg/day (round to nearest whole syringe)	S/C	n/a
Dose rounding: Fludarabine doses ≤50mg to the nearest 2.5mg and doses >50mg to the nearest 5mg Melphalan to the nearest 5mg				
[a]All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation).				
[b]When reconstituted melphalan has a very short expiry time. It must be administered once it reaches the ward due to instability. Melphalan is not compatible with glucose solutions. **(Refer to local policy for guidance on stability and shelf life to co-ordinate administration with pharmacy compounding)**				

ELIGIBILITY:

- Indications as above
- Medical assessment as per SJH BMT assessment form

EXCLUSIONS:

- Hypersensitivity to fludarabine, melphalan, alemtuzumab or any of the excipients.

PRESCRIPTIVE AUTHORITY:

- The treatment plan must be initiated by a Haematology Consultant working in the area of stem cell transplantation in a unit suitable for carrying out this treatment.

TESTS:

- Baseline and regular tests in accordance with SJH Haematopoietic Stem Cell Transplant work-up protocols

Disease monitoring:
Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Haematology Consultant.
- **Chemotherapy dosing in obese adult patients:** For patients with a BMI > 30kg/m^2 please refer to 'Chemotherapy Dosing in Obese Adult Stem Cell Transplant Recipients – Guidelines' for guidance on individual drug dosing as per SJH policy available on the SJH intranet.
- **Renal and Hepatic Impairment:**
    - Dose modifications are generally not undertaken in conditioning regimens.
    - Discuss with the consultant if hepatic impairment or if creatinine clearance is <70ml/min for advice on fludarabine dosing. Guidance to inform this discussion available at: U:\PHARMCOMP\Clinical\haematology\Haematology Drugs\Fludarabine
    - Consult the following resources to inform any renal or hepatic dose modification discussions:
        - Summary of product characteristics (SPC) available at http://www.hpra.ie
        - Krens et al Lancet Oncol 2019;20(4) e200-e207 "Dose Recommendations for anticancer drugs in patients with renal or hepatic impairment" available at https://pubmed.ncbi.nlm.nih.gov/30942181/
        - UCHL renal impairment guidelines and hepatic impairment guidelines available on SJH intranet

SUPPORTIVE CARE:

Antiemetics

Table 1: Recommended SJH regimen specific Antiemetics

Prevention of acute emesis			Prevention of delayed emesis			Comments
Drug	**Dose**	**Admin day**	**Drug**	**Dose**	**Admin day**	Dexamethasone with melphalan only
Aprepitant	125mg PO	-2	Aprepitant	80mg PO	-1 and 0	
Dexamethasone	6mg PO	-2	Dexamethasone	4mg PO	-1, 0 and +1	
Ondansetron	8mg PO/IV TDS	-2				

Alemtuzumab Premedication

Prior to alemtuzumab therapy (i.e. 60 minutes pre-therapy), the following should be administered:

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

Melphalan hydration

- Sodium chloride 0.9% must be given at a rate of 125ml/m^2/hour for 2 hours pre-melphalan and for 6 hours post-melphalan

Other Supportive Care

Table 2: Recommended SJH Regimen Specific Antiemetics

GvHD prophylaxis: Refer to signed off BMT assessment form for confirmed **choice and target level** of immunosuppression	**Ciclosporin** • Ciclosporin 3mg/kg once daily IV over 6 hours from day -1 • The equivalent oral dose is: (Total IV dose x 0.67) twice daily PO • Target levels: 100-150 micrograms/litre	**Tacrolimus** • 0.03mg/kg once daily IV over 22 hours, starting from day -1 • The equivalent oral dose is: (Total IV dose) twice daily PO • Target levels: 5-10 nanograms/ml
GvHD and VOD prophylaxis	• Ursodeoxycholic acid 250mg TDS PO • Continue until day +90	

HSV prophylaxis	All patients should receive the following until CD4 count >200/microlitre: • Valaciclovir 500mg once daily PO **or** • Aciclovir 250mg TDS IV (if oral route not available or ANC < $0.5x10^9$/L) Patients with an active herpes infection should receive the following: • Valaciclovir 1g TDS PO **or** • Aciclovir 10mg/kg TDS IV (if oral route not available)
CMV prophylaxis Prescribe for all CMV seropositive recipients	**Patients receiving CMV prophylaxis with letermovir also require HSV prophylaxis above** • Letermovir 240mg once daily PO/IV, as appropriate, starting Day +1 if patient is receiving ciclosporin immunosuppression • Letermovir 480mg once daily PO/IV, as appropriate, starting Day +1 if patient is receiving tacrolimus immunosuppression • Letermovir via the oral route is first line. • Letermovir IV at the same oral dose should be prescribed only where the patient cannot tolerate oral or where there are concerns around absorption. • CMV prophylaxis is usually continued until day +100 Patients should bring their oral letermovir supply with them on admission. High tech prescription will have been provided to patient at their counselling appointment pre-admission. Liaise with transplant pharmacist if any supply issues arise. When ANC>1.0 x 10^9/L, pre-emptive monitoring (9mls in EDTA [purple tube] (Tuesday and Fridays) should be carried out for CMV reactivation/infection in *all* patients
Antifungal prophylaxis Refer to signed off BMT assessment form for confirmed choice of antifungal prophylaxis	When ANC<0.5 x 10^9/L or if patients on high dose steroids • Liposomal amphotericin 1mg/kg once daily IV Mon/Wed/Fri **Or** • Caspofungin 70mg/kg once daily IV Mon/Wed/Fri If at higher risk due to prior possible/probable fungal infection: • Liposomal amphotericin 1mg/kg once daily IV **Or** • Caspofungin 70mg once daily IV if >80kg **Or** • Caspofungin 70mg once daily IV on day 1 of treatment and 50mg once daily IV thereafter if <80kg

PJP prophylaxis	First line therapy • Co-trimoxazole 960mg BD Mon/Wed/Fri PO • Commence only on engraftment when ANC > $1.0x10^9$/L if appropriate Second line therapy (if allergic to co-trimoxazole or contraindicated): *PJP Prophylaxis and T. gondii IgG NEGATIVE:* • Pentamidine 300mg nebule and salbutamol 2.5mg nebule pre-pentamidine, every 4 weeks **plus** • Phenoxymethylpenicillin 333mg BD daily PO Continue the phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/haemophilus titres *PJP prophylaxis and T.gondii IgG POSITIVE:* • Atovaquone 750mg BD PO plus • Pyrimethamine 25mg once daily PO plus • Folinic acid 15mg once daily PO plus • Phenoxymethylpenicillin 333mg BD daily PO Continue the phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/haemophilus titres Please note: If a patient is to be discharged on atovaquone, pyrimethamine or folinic acid, please contact pharmacy in advance to arrange supply and funding through a community drugs scheme
Mouthcare:	Mucositis WHO grade < 2: • Sodium chloride 0.9% 10ml QDS mouthwash • Nystatin 1ml QDS PO (use 15 minutes after sodium chloride 0.9% mouthwash) Mucositis WHO grade ≥2: • Chlorhexidine digluconate 0.12% (Kin®mouthwash) 10mls QDS mouthwash • Nystatin 1ml QDS PO (use 15 minutes after Kin® mouthwash)
Gastroprotection:	• Lansoprazole 30mg /omeprazole 40mg once daily PO **Or** • Esomeprazole 40mg once daily IV (if oral route not available)
Folate supplementation:	• Folinic acid 15mg once daily IV commenced from day + 2 onwards • Switch to folic acid 5mg once daily PO when oral route is available.

Vitamin K supplementation	Beginning on day + 2 post stem cell transplant • Vitamin K (phytomenadione) 10mg once weekly IV
Prevention of vaginal bleeding;	If required for menstruating female patients until platelets > 50 x10^9/L • Norethisterone 5mg TDS PO if >55Kg • Norethisterone 5mg BD PO if <55kg
Tumour Lysis syndrome	Consider allopurinol in active disease pre transplant • Allopurinol 300mg once daily PO for 5-7 days and review
Hepatitis B prophylaxis/treatment	A virology screen is completed as part of transplant workup. Hepatitis B prophylaxis or treatment may be initiated in consultation with a Virology Consultant or Hepatology Consultant if required. Options may include: • Lamivudine 100mg once daily PO **Or** • Entecavir 500mcg once daily PO
Prevention of constipation	Consider laxatives if appropriate e.g. • Senna two tablets (15mg) nocte PO while on ondansetron.
Antibiotic standing order	Antibiotic standing order should be prescribed for neutropenic sepsis/neutropenic fever based on previous microbiology and renal function • Piptazobactam 4.5g QDS IV **Plus** • Amikacin* 15mg/kg once daily IV *Ciprofloxacin 400mg BD IV may be considered instead of amikacin in cases of renal impairment Refer to local Antimicrobial Guidelines for antibiotic choice where a patient is allergic to any of the above
Magnesium and Potassium Standing order:	Magnesium and Potassium Standing order: Magnesium and potassium standing orders should be prescribed for all transplant patients in accordance with stem cell unit practice as indicated on EPMAR.
VTE prophylaxis	Consider VTE prophylaxis in accordance with local SJH policy
Bone Health	Consider calcium and vitamin D supplementation prior to discharge for patients who are on high dose steroids. Other medications for maintenance of bone health may need to be considered as appropriate. • Calcium carbonate and colecalciferol (Caltrate® 600mg/400unit) one tablet BD

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

- Please refer to the relevant Summary of Product Characteristics and SJH Stem Cell Transplant Programme PPGs for full details.

DRUG INTERACTIONS:

- The relevant Summary of Product Characteristics and current drug interaction databases should be consulted.

REFERENCES:

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Version	Date	Amendment	Approved By
1	06/08/2021		SJH Stem Cell Transplant Group
1a	09/07/2024	Extension of review date as agreed with clinical reviewer	NCCP

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.