Fludarabine/ Melphalan with-post transplant cycloPHOSphamide Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	HSE approved reimbursement status*
Reduced Intensity Conditioning with Fludarabine and Melphalan for Mismatched Unrelated Donors or physician choice for myeloid and lymphoid malignancies.	C91, C92	00868a	N/A

*For post 2012 indications only

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Conditioning chemotherapy is administered over 6 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	100mL NaCl 0.9% over 30 minutes
-2	Melphalan[b]	140mg/m^2	IV push	Slow IV push into side arm of a fast flowing 0.9% NaCl infusion over 15-30 minutes
0	Stem Cell Re-infusion			
+3, +4 (Start at 09.30)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion
+3, +4 (first dose between 60 and 72 hours after the start of the PBSC infusion) (Start at 10:00)	cycloPHOSphamide*	50 mg/kg	IV infusion	1000mL NaCl 0.9% over 3 hours
+3, +4 (Start at 13:00)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion
+3, +4 (Start at 16:00)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion

+3, +4 (Start at 19:00)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion
+3, +4 (Start at 22:00)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion
+4, +5 (Start at 02:00)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion
+4, +5 (Start at 06:00)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion
+5 (Start at 10:00)	Mesna	20mg/kg	Slow IV push	Into side arm of a fast flowing NaCl 0.9% infusion
[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)**				
Dose rounding: Fludarabine doses ≤50mg to the nearest 2.5mg and doses >50mg to the nearest 5mg Melphalan to the nearest 5mg Mesna to the nearest 100mg cycloPHOSphamide to the nearest 20mg				

Note: Administration volumes and fluids have been standardised to facilitate electronic prescribing system builds.

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to fludarabine, melphalan, cycloPHOSphamide 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

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Haematology Consultant.

cycloPHOSphamide Dosing:

- The cycloPHOSphamide dose is to be calculated using Ideal Body Weight.
  However, if Actual Body Weight < Ideal Body Weight, use Actual Body Weight. (Refer to local policy).

Chemotherapy dosing in obese adult patients:

- For patients with a BMI > 30kg/m2 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/minute for advice on fludarabine dosing. Guidance to inform this discussion available on SJH Intranet
- Consult the following resources to inform any renal or hepatic dose modification discussions:
  - Summary of product characteristics (SmPC) available at http://www.hpra.ie
  - Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
  - UCHL renal impairment guidelines and hepatic impairment guidelines available on SJH intranet

SUPPORTIVE CARE:

- No systemic immunosuppressive agents, such as corticosteroids, should be given from day 0 until 24 hours after the completion of the post-transplant cycloPHOSphamide (Day +5) this includes dexAMETHasone as an antiemetic from day -1 to day +5.

Antiemetics

Table 1: Recommended SJH Regimen Specific Antiemetics

Prevention of acute nausea and vomiting			**Prevention of delayed nausea and vomiting**		
Drug	**Dose**	**Admin Day**	**Drug**	**Dose**	**Admin Day**
Aprepitant	125mg PO	**-2 and +3**	Aprepitant	80mg PO	**-1, 0, +4, +5, +6**
dexAMETHasone	6 mg PO	**-2**			
Ondansetron	8mg PO/IV TDS	**-2 to +7**			

Melphalan hydration

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

cycloPHOSphamide hydration and diuresis

- Start pre–hydration 4 hours before cycloPHOSphamide begins (usually on day +3). The recommended hydration regimen is NaCl 0.9% 2-3L/m^2 over 24 hours.
- Continue hydration for at least 24 hours after completion of cycloPHOSphamide.
- Diuretics may be indicated for positive fluid balance, weight gain or declining urine production (<100mL/m^2/hour).
- Furosemide 20-40mg IV PRN should be prescribed.

OTHER SUPPORTIVE CARE:

Table 2: Recommended SJH Specific Supportive Care

GvHD prophylaxis Refer to signed off BMT assessment form for confirmed ***choice and target level*** of immunosuppression	**Tacrolimus** • Tacrolimus 0.03mg/kg once daily IV over 22 hours from day +5 • The equivalent oral dose is: Total IV dose, twice daily PO • Target levels: 5-10 nanogram/mL	**Mycophenolate Mofetil** • Mycophenolate Mofetil 15mg/kg BD PO/IV from day +5. **Maximum *total daily* dose not to exceed 3g.** • IV dose is the same as PO given over 2 hours in 5% glucose at a concentration of 6mg/mL • If renal failure do not exceed dose of 1gm bd. (SmPC <25mL/minute) • No dose adjustment for liver disease. • MMF dosing should be monitored and altered as clinically appropriate. Stop MMF at day +35 unless active GvHD present (discuss with consultant).
VOD prophylaxis	• Ursodeoxycholic acid 250mg TDS PO • Continue until day +90	
HSV prophylaxis	All patients should receive the following until CD4 count >200/µL: • 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 preadmission. Liaise with transplant pharmacist if any supply issues arise. When ANC>1.0 x 109 /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	When ANC <$0.5x10^9$/L or if patients on high dose steroids • Ambisome® 1mg/kg once daily IV Mon/Wed/Fri or • Caspofungin 70mg once daily IV Mon/Wed/Fri	

Refer to signed off BMT assessment form for confirmed choice of antifungal prophylaxis	If at higher risk due to prior possible/probable fungal infection: • Ambisome® 1mg/kg once daily IV or • Caspofungin 70mg once daily IV if >80kg or Caspofungin 70mg once daily IV on day 1 of treatment followed by 50mg once daily IV thereafter if <80kg
PCP prophylaxis	1st line therapy • Co-trimoxazole 960mg BD Mon/Wed/Fri PO Commence only on engraftment when ANC > $1.0x10^9$/L if appropriate 2nd line therapy (if allergic to co-trimoxazole or contraindicated): *PCP Prophylaxis and T. gondii IgG NEGATIVE* • Pentamidine 300mg nebule and salbutamol 2.5mg nebule pre-pentamidine, every 4 weeks plus • Calvepen® 333mg BD daily PO Continue the Calvepen® until patients have been revaccinated and have adequate pneumococcal/Haemophilus titres *PCP Prophylaxis and T gondii IgG POSITIVE* • Atovaquone 750mg BD PO plus • Pyrimethamine 25mg once daily PO plus • Folinic acid 15mg once daily PO plus • Calvepen® 333mg BD daily PO Continue the Calvepen® 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: • NaCl 0.9% 10mL QDS mouthwash • Nystatin 1mL QDS PO (use 15 minutes after NaCl 0.9% mouthwash) Mucositis WHO grade ≥ 2: • Chlorhexidine digluconate 0.12% (Kin®) 10mL QDS PO • 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 500 micrograms 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 Antimicrobial Guidelines in the Prescriber's Capsule for antibiotic choice where a patient is allergic to any of the above
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 SJH policy

ADVERSE EFFECTS/ REGIMEN SPECIFIC COMPLICATIONS

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

DRUG INTERACTIONS:

- Current SmPC and drug interaction databases should be consulted for information.

REFERENCES:

1. A Randomized, Multicenter, Phase III Trial of Tacrolimus/Methotrexate versus Post-Transplant Cyclophosphamide/Tacrolimus/Mycophenolate Mofetil in Non-Myeloablative/Reduced Intensity Conditioning Allogeneic Peripheral Blood Stem Cell Transplantation, National Institutes of Health National Heart, Lung, and Blood Institute National Cancer Institute BMT CTN Protocol 1703/1801 Version 4.0
2. Giraud E L, Lijster B D, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment: an update. Available at: https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(23)00216-4/fulltext
3. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at:

https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
4. Fludarabine 50mg (Fludara®) SmPc. Accessed Aug 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0611-004-001_11112019115658.pdf
5. Melphalan 50mg (Alkeran®) SmPC. Accessed Aug 2024. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1691-004-001_08062023145649.pdf
6. cycloPHOSphamide Injection 500 mg (Endoxana®) SmPC. Accessed Aug 2024.Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-001_21122018112107.pdf

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1	13/01/2025		Dr Catherine Flynn

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