

## Fludarabine/Melphalan/Alemtuzumab-RIC-MUD

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Reduced intensity conditioning for matched unrelated donor allogeneic stem cell transplant in patients with lymphoproliferative disorders.	C91	00625a	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 <sup>a</sup>	30mg/m <sup>2</sup>	IV infusion	100mls sodium chloride 0.9% over 30 minutes
-2	Melphalan <sup>b</sup>	140mg/ m <sup>2</sup>	IV push	Give as an IV push over 15-30 minutes via side-arm of a fast flowing sodium chloride 0.9% infusion
-2,-1	Alemtuzumab	30mg	IV infusion	100mls sodium chloride 0.9% over 6 hours
<b>0</b>	Stem cell infusion			
<b>Start +6</b>  (until ANC > 1.0X10 <sup>9</sup> /L for two consecutive days)	Filgrastim (G-CSF)	5mcg/kg/day  (round to nearest whole syringe)	S/C	n/a
<b>Dose rounding:</b> Fludarabine doses ≤50mg to the nearest 2.5mg and doses >50mg to the nearest 5mg Melphalan to the nearest 5mg				
<sup>a</sup> All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation).				
<sup>b</sup> 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. <b>(Refer to local policy for guidance on stability and shelf life to co-ordinate administration with pharmacy compounding)</b>				

### ELIGIBILITY:

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

### EXCLUSIONS:

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

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## 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<sup>2</sup> 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/>
    - UCL renal impairment guidelines and hepatic impairment guidelines available on SJH intranet

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## 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	
Aprepitant	125mg PO	-2	Aprepitant	80mg PO	-1 and 0	Dexamethasone with melphalan only
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<sup>2</sup>/hour for 2 hours pre-melphalan and for 6 hours post-melphalan

### Other Supportive Care

**Table 2: Recommended SJH regimen specific supportive care**

<b>GvHD prophylaxis:</b>  Refer to signed off BMT assessment form for confirmed <b>choice and target level</b> of immunosuppression	<b>Ciclosporin</b> <ul style="list-style-type: none"> <li>• Ciclosporin 3mg/kg once daily IV over 6 hours from day -1</li> <li>• The equivalent oral dose is: (Total IV dose x 0.67) twice daily PO</li> <li>• Target levels: 100-150micrograms/litre</li> </ul>	<b>Tacrolimus</b> <ul style="list-style-type: none"> <li>• 0.03mg/kg once daily IV over 22 hours, starting from day -1</li> <li>• The equivalent oral dose is: (Total IV dose) twice daily PO</li> <li>• Target levels: 5-10 nanograms/ml</li> </ul>
<b>GvHD and VOD prophylaxis</b>	<ul style="list-style-type: none"> <li>• Ursodeoxycholic acid 250mg TDS PO</li> <li>• Continue until day +90</li> </ul>	

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<p><b>HSV prophylaxis</b></p>	<p>All patients should receive the following until CD4 count &gt;200/microlitre:</p> <ul style="list-style-type: none"> <li>Valaciclovir 500mg once daily PO</li> <li>Or</li> <li>Aciclovir 250mg TDS IV (if oral route not available or ANC &lt; 0.5x10<sup>9</sup>/L)</li> </ul> <p>Patients with an active herpes infection should receive the following:</p> <ul style="list-style-type: none"> <li>Valaciclovir 1g TDS PO</li> <li>or</li> <li>Aciclovir 10mg/kg TDS IV (if oral route not available)</li> </ul>
<p><b>CMV prophylaxis</b></p> <p>Prescribe for all CMV seropositive recipients</p>	<p><b>Patients receiving CMV prophylaxis with letermovir also require HSV prophylaxis above</b></p> <ul style="list-style-type: none"> <li>Letermovir 240mg once daily PO/IV, as appropriate, starting Day +1 if patient is receiving ciclosporin immunosuppression</li> <li>Letermovir 480mg once daily PO/IV, as appropriate, starting Day +1 if patient is receiving tacrolimus immunosuppression</li> <li>Letermovir via the oral route is first line.</li> <li>Letermovir IV at the same oral dose should be prescribed only where the patient cannot tolerate oral or where there are concerns around absorption</li> <li>CMV prophylaxis is usually continued until day +100</li> </ul> <p>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.</p> <p>When ANC &gt; 1.0 x 10<sup>9</sup>/L, pre-emptive monitoring (9mls in EDTA [purple tube] (Tuesday and Fridays) should be carried out for CMV reactivation/infection in <i>all</i> patients</p>
<p><b>Antifungal prophylaxis</b></p> <p>Refer to signed off BMT assessment form for confirmed choice of antifungal prophylaxis</p>	<p>When ANC &lt; 0.5 x 10<sup>9</sup>/L or if patients on high dose steroids</p> <ul style="list-style-type: none"> <li>Liposomal amphotericin 1mg/kg once daily IV Mon/Wed/Fri</li> <li>Or</li> <li>Caspofungin 70mg/kg once daily IV Mon/Wed/Fri</li> </ul> <p>If at higher risk due to prior possible/probable fungal infection:</p> <ul style="list-style-type: none"> <li>Liposomal amphotericin 1mg/kg once daily IV</li> <li>Or</li> <li>Caspofungin 70mg once daily IV if &gt;80kg</li> <li>Or</li> <li>Caspofungin 70mg once daily IV on day 1 of treatment and 50mg once daily IV thereafter if &lt;80kg</li> </ul>

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<p><b>PJP prophylaxis</b></p>	<p><u>First line therapy</u></p> <ul style="list-style-type: none"> <li>• Co-trimoxazole 960mg BD Mon/Wed/Fri PO</li> <li>• Commence only on engraftment when ANC &gt; 1.0x10<sup>9</sup>/L if appropriate</li> </ul> <p><u>Second line therapy (if allergic to co-trimoxazole or contraindicated):</u> <i>PJP Prophylaxis and T. gondii IgG NEGATIVE</i></p> <ul style="list-style-type: none"> <li>• Pentamidine 300mg nebule and salbutamol 2.5mg nebule pre-pentamidine, every 4 weeks</li> <li>• <b>plus</b></li> <li>• Phenoxymethylpenicillin 333mg BD daily PO</li> </ul> <p>Continue the phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/haemophilus titres</p> <p><i>PJP prophylaxis and T.gondii IgG POSITIVE:</i></p> <ul style="list-style-type: none"> <li>• Atovaquone 750mg BD PO plus</li> <li>• Pyrimethamine 25mg once daily PO plus</li> <li>• Folinic acid 15mg once daily PO plus</li> <li>• Phenoxymethylpenicillin 333mg BD daily PO</li> </ul> <p>Continue the Phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/haemophilus titres</p> <p>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</p>
<p><b>Mouthcare:</b></p>	<p>Mucositis WHO grade &lt; 2:</p> <ul style="list-style-type: none"> <li>• Sodium chloride 0.9% 10ml QDS mouthwash</li> <li>• Nystatin 1ml QDS PO (use 15 minutes after sodium chloride 0.9% mouthwash)</li> </ul> <p>Mucositis WHO grade ≥2:</p> <ul style="list-style-type: none"> <li>• Chlorhexidine digluconate 0.12% (Kin<sup>®</sup> mouthwash) 10mls QDS mouthwash</li> <li>• Nystatin 1ml QDS PO (use 15 minutes after Kin<sup>®</sup> mouthwash)</li> </ul>
<p><b>Gastro protection:</b></p>	<ul style="list-style-type: none"> <li>• Lansoprazole 30mg /omeprazole 40mg once daily PO</li> <li>• <b>Or</b></li> <li>• Esomeprazole 40mg once daily IV (if oral route not available)</li> </ul>
<p><b>Folate supplementation:</b></p>	<ul style="list-style-type: none"> <li>• Folinic acid 15mg once daily IV commenced from day + 2 onwards</li> <li>• Switch to folic acid 5mg once daily PO when oral route is available.</li> </ul>
<p><b>Vitamin K supplementation</b></p>	<p>Beginning on day + 2 post stem cell transplant</p> <ul style="list-style-type: none"> <li>• Vitamin K (phytomenadione) 10mg once weekly IV</li> </ul>
<p><b>Prevention of vaginal bleeding;</b></p>	<p>If required for menstruating female patients until platelets &gt; 50 x10<sup>9</sup>/L</p> <ul style="list-style-type: none"> <li>• Norethisterone 5mg TDS PO if &gt;55kg</li> <li>• Norethisterone 5mg BD PO if &lt;55kg</li> </ul>
<p><b>Tumour Lysis syndrome</b></p>	<p>Consider allopurinol in active disease pre transplant</p> <ul style="list-style-type: none"> <li>• Allopurinol 300mg once daily PO for 5-7 days and review</li> </ul>

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<b>Hepatitis B prophylaxis/treatment</b>	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: <ul style="list-style-type: none"> <li>Lamivudine 100mg once daily PO</li> <li><b>Or</b></li> <li>Entecavir 500mcg once daily PO</li> </ul>
<b>Prevention of constipation</b>	Consider laxatives if appropriate e.g. <ul style="list-style-type: none"> <li>Senna two tablets (15mg) nocte PO while on ondansetron.</li> </ul>
<b>Antibiotic standing order</b>	Antibiotic standing order should be prescribed for neutropenic sepsis/neutropenic fever based on previous microbiology and renal function <ul style="list-style-type: none"> <li>Piptazobactam 4.5g QDS IV</li> <li><b>Plus</b></li> <li>Amikacin* 15mg/kg once daily IV</li> </ul> <p>*Ciprofloxacin 400mg BD IV may be considered instead of amikacin in cases of renal impairment</p> <p>Refer to local SJH Antimicrobial Guidelines for antibiotic choice where a patient is allergic to any of the above</p>
<b>Magnesium and Potassium Standing order:</b>	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.
<b>VTE prophylaxis</b>	Consider VTE prophylaxis in accordance with local SJH policy
<b>Bone Health</b>	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. <ul style="list-style-type: none"> <li>Calcium carbonate and colecalciferol (Caltrate® 600mg/400unit) one tablet BD</li> </ul>

## 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.

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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](mailto:oncologydrugs@cancercontrol.ie).

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