# Cyclophosphamide/Total Body Irradiation (TBI)–MAC–Mismatched Sibling Donor

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| Myeloablative conditioning (MAC) for mismatched sibling donor allogeneic stem cell transplant in patients with lymphoid disorders | C91 | 00630a | Hospital |

## TREATMENT:

Conditioning chemotherapy is administered over **8 days**. Stem cells are infused on **day 0.**
Facilities to treat anaphylaxis MUST be present when conditioning therapy and stem cells are administered.

| Day (time) | Drug | Dose | Route | Diluent & Rate |
|---|---|---|---|---|
| **-8, -7** (09.30)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-8, -7** (10.00)* | Cyclophosphamide | 60mg/kg | IV infusion | 1000ml sodium chloride 0.9% over 3 hours |
| **-8, -7** (13.00)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-8, -7** (16.00)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-8, -7** (19.00)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-8, -7** (22.00)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-7, -6** (02.00)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-7, -6** (06.00)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-6** (10.00)* | Mesna | 24mg/kg | Slow IV push | Into side arm of fast flowing sodium chloride 0.9% infusion |
| **-6,-5,-4** | Fractionated TBI | Twice Daily | n/a | n/a |
| **-3** | ATG Grafalon® | 10mg/kg | IV infusion | (see note)[a] ml sodium chloride 0.9% over 12 hours[b] |
| **-2, -1** | ATG Grafalon® | 10mg/kg | IV infusion | (see note)[a] ml sodium chloride 0.9% over 10 hours[b] |
| **0** | Stem cell infusion | | | |
| **+1 (at Least 24 hours post completion of stem cell infusion)** | Methotrexate[c] | 15mg/m$^2$ | IV infusion | 50ml sodium chloride 0.9% over 10 minutes |
| **+3, +6, +11** | Methotrexate | 10mg/m$^2$ | IV infusion | 50ml sodium chloride 0.9% over 10 minutes |

**Dose rounding:**
Mesna to the nearest 100mg,
Cyclophosphamide to the nearest 20mg,
ATG Grafalon® to the nearest 20mg
Methotrexate to the nearest 2.5mg



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|---|
| [a]Each ml of ATG Grafalon® should be diluted with 6ml of sodium chloride 0.9% in accordance with SPC. Pharmacy to complete volume. |
| [b]Patient monitoring is required during the ATG Grafalon® infusion: BP, pulse, respiration and temperature at 15, 30 and then 60 minute intervals for the duration of the infusion.<br>If a reaction occurs, the infusion should be slowed. Chills and fever generally respond to antihistamines, antipyretics or corticosteroids. If the patient becomes hypotensive or experiences chest or back pain, indicating anaphylaxis, the infusion should be stopped and the medical team contacted immediately.<br>Platelets should be >50x$10^9$/L pre day 1 ATG Grafalon® treatment. If the patient has no reaction to ATG, platelets can be maintained at >30x$10^9$/L for the remaining days of ATG administration. Platelets should be maintained at >50x$10^9$/L in the setting of clinically symptomatic bleeding |
| [c]Day +1 methotrexate should be administered at least 24 hours post completion of stem cell infusion.<br>In the event where this timing results in methotrexate being infused during the night, it is reasonable to reschedule the administration time of the day +3 methotrexate dose to the next morning, to avoid administration during the night. The amended administration timing can then be maintained for subsequent methotrexate doses. |
| *Denotes recommended administration times |

## ELIGIBILITY:

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

## EXCLUSIONS:

- Hypersensitivity to cyclophosphamide, mesna, ATG Grafalon®, methotrexate or any of the excipients
- Pregnancy and lactation

## 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.



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## 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 the creatinine clearance is < 50 ml/min or if abnormal hepatic function.
  - 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 nausea and vomiting | | | Prevention of delayed nausea and vomiting | | | Comment |
|---|---|---|---|---|---|---|
| **Drug** | **Dose** | **Admin Day** | **Drug** | **Dose** | **Admin Day** | |
| Dexamethasone | 12mg PO | -8, -7 | Dexamethasone | 8mg PO | -6, -5, -4 | Exclude aprepitant due to interaction with cyclophosphamide |
| Ondansetron | 8mg PO/IV TDS | -8, -7 | | | | |

### Cyclophosphamide hydration and diuresis:

- Pre stem cell infusion: Start pre-hydration at 6.00 am on Day -8
  - Recommended hydration regimen is sodium chloride 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$^2$/hr)
  - Furosemide 20-40mg IV PRN should be prescribed

### ATG Grafalon® supportive medications:

- Methylprednisolone 2mg/kg once daily IV 90mins before commencing ATG on Day -3 to Day -1
- Chlorphenamine 10mg IV 30mins before commencing ATG on Day -3 to Day -1
- Prednisolone 1mg/kg once daily PO (or an equivalent IV alternative starting on Day 0 and continuing for 5 days
- Taper to zero over next 5 days to prevent serum sickness



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## Other Supportive Care:

**Table 2: Other Supportive Medication**

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|---|---|
| **GvHD prophylaxis**<br>Refer to signed off BMT assessment form for confirmed **choice and target level** of immunosuppression | **Tacrolimus**<br>Tacrolimus 0.03mg/kg once daily IV over 22 hours from day -1<br>• The equivalent oral dose is: (Total IV dose) twice daily PO<br>• Target levels: 5-10 nanograms/ml |
| **GvHD and VOD prophylaxis** | • Ursodeoxycholic acid 250mg TDS PO<br>• Continue until day +90 |
| **HSV prophylaxis** | All patients should receive the following until CD4 count >200/microlitre:<br>• Valaciclovir 500mg once daily PO<br>**or**<br>• Aciclovir 250mg TDS IV (if oral route not available or ANC < $0.5X10^9$/L)<br><br>Patients with an active herpes infection should receive the following:<br>• Valaciclovir 1g TDS PO<br>**or**<br>• Aciclovir 10mg/kg TDS IV (if oral route not available) |
| **CMV prophylaxis**<br><br>Prescribe for all CMV seropositive recipients | **Patients receiving CMV prophylaxis with letermovir also require HSV prophylaxis above**<br>• Letermovir 480mg once daily PO/IV, as appropriate, starting Day +1 if patient is receiving tacrolimus immunosuppression<br>• Letermovir via the oral route is first line.<br>• Letermovir IV at the same oral dose should be prescribed only where the patient cannot tolerate oral or where there are concerns around absorption.<br>• CMV prophylaxis is usually continued until day +100<br><br>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.<br><br>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**<br>Refer to signed off BMT assessment form for confirmed choice of antifungal prophylaxis | When ANC <$0.5x10^9$/L or if patients on high dose steroids:<br>• Liposomal amphotericin 1mg/kg once daily IV Mon/Wed/Fri<br>**or**<br>• Caspofungin 70mg once daily IV Mon/Wed/Fri<br><br>If at higher risk due to prior possible/probable fungal infection:<br>• Liposomal amphotericin 1mg/kg once daily IV<br>**or**<br>• Caspofungin 70mg once daily IV if >80kg<br>**or**<br>• Caspofungin 70mg once daily IV on day 1 of treatment followed by 50mg once daily IV thereafter if <80kg |



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| **PJP prophylaxis** | 1st line therapy:<br>• Co-trimoxazole 960mg BD Mon/Wed/Fri PO<br>• Commence only on engraftment when ANC > $1.0x10^9$/L if appropriate<br><br>2nd line therapy (if allergic to co-trimoxazole or contraindicated):<br>*PJP Prophylaxis and T. gondii IgG NEGATIVE:*<br>• Pentamidine 300mg nebule and salbutamol 2.5mg nebule pre-pentamidine, every 4 weeks<br>**plus**<br>• Phenoxymethylpenicillin 333mg BD daily PO<br><br>Continue the phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/haemophilus titres<br><br>*PJP Prophylaxis and T gondii IgG POSITIVE:*<br>• Atovaquone 750mg BD PO plus<br>• Pyrimethamine 25mg once daily PO plus<br>• Folinic acid 15mg once daily PO plus<br>• Phenoxymethylpenicillin 333mg BD daily PO<br><br>Continue the phenoxymethylpenicillin until patients have been revaccinated and have adequate pneumococcal/haemophilus titres<br><br>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:<br>• Sodium chloride 0.9% 10ml QDS mouthwash<br>• Nystatin 1ml QDS PO (use 15 minutes after sodium chloride 0.9% mouthwash)<br>Mucositis WHO grade ≥ 2:<br>• Chlorhexidine digluconate 0.12% (Kin® mouthwash) 10mls QDS mouthwash<br>• Nystatin 1ml QDS PO (use 15 minutes after Kin® mouthwash) |
| **Gastroprotection** | • Lansoprazole 30mg / omeprazole 40mg once daily PO<br>**or**<br>• Esomeprazole 40mg once daily IV (if oral route not available) |
| **Folate supplementation** | **Methotrexate is included as GvHD prophylaxis. Folinic acid should not be administered on the same days as methotrexate.**<br>The first dose of folinic acid must be administered at a minimum of 24 hours post completion of methotrexate. Prescribe as outlined below:<br>• Folinic acid 15mg once daily IV on days **+2,+4,+5,+7,+8,+9,+10 and +12 onwards**<br>• Switch to folic acid 5mg once daily PO when oral route is available |
| **Vitamin K supplementation** | Beginning on day +2 post stem cell transplant<br>• Vitamin K (phytomenadione) 10mg once weekly IV |
| **Prevention of vaginal bleeding** | If required for menstruating female patients until platelets > 50 $x10^9$/L<br>• Norethisterone 5mg TDS PO if >55Kg<br>• Norethisterone 5mg BD PO if <55kg |



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| | |
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| **Tumour Lysis syndrome** | Consider allopurinol in active disease pre transplant<br>• 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.<br><br>Options may include:<br>• Lamivudine 100mg once daily PO<br>**or**<br>• Entecavir 500mcg once daily PO |
| **Prevention of constipation** | Consider laxatives if appropriate e.g.<br>• 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<br>• Piptazobactam 4.5g QDS IV<br>**plus**<br>• Amikacin* 15mg/kg once daily IV<br><br>*Ciprofloxacin 400mg BD IV may be considered instead of amikacin in cases of renal impairment<br><br>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 |
| **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.<br>• 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.



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Comments and feedback welcome at oncologydrugs@cancercontrol.ie.



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