Busulfan/Cyclophosphamide – MAC – SIB

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Myeloablative conditioning for sibling donor allogeneic stem cell transplant in patients with myeloid disorders.	C92	00641a	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 (time)	Drug	Dose	Route	Diluent & Rate
-7,-6,-5,-4 (16.30)*	Busulfan[a]	0.8mg/kg	IV infusion	(see note)[b] ml of sodium chloride 0.9% over 2 hours
-7,-6,-5,-4 (22.30)*	Busulfan[a]	0.8mg/kg	IV infusion	(see note)[b] ml of sodium chloride 0.9% over 2 hours
-6,-5,-4,-3 (04.00)*	Busulfan[a]	0.8mg/kg	IV infusion	(see note)[b] ml of sodium chloride 0.9% over 2 hours
-6,-5,-4,-3 (10.30)*	Busulfan[a]	0.8mg/kg	IV infusion	(see note)[b] ml of sodium chloride 0.9% over 2 hours
NB: IV busulfan expires after 15 hours, infusion must begin at time specified				
-2 -1 (09.30)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
-2, -1 (10.00)*	Cyclophosphamide	60mg/kg	IV infusion	1000ml sodium chloride 0.9% over 3 hours
-2 -1 (13.00)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
-2 -1 (16.00)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
-2 -1 (19.00)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
-2 -1 (22.00)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
-1, 0 (02.00)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
-1, 0 (06.00)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
0 (10.00)*	Mesna	24mg/kg	Slow IV push	Into side arm of fast flowing sodium chloride 0.9% infusion
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	Methotrexate	10mg/m^2	IV infusion	50ml sodium chloride 0.9% over 10 minutes

Dose rounding:
Busulfan to the nearest 1.2mg if <60mg, to nearest 6mg if >60mg. Oral busulfan available as 2mg and 25mg tablets.
Mesna to the nearest 100mg,
Cyclophosphamide to the nearest 20mg,
Methotrexate to the nearest 2.5mg

[a]If a problem with an infusion bag (i.e. leaking bag, short expiry) is discovered outside of 8.30am-5pm, an oral dose of busulfan 1mg/kg equivalent to the intravenous dose will be available from the MDA press on Denis Burkitt Ward. This can only be used after discussion with a haematology consultant and must be prescribed by haematology registrar or consultant on a chemotherapy prescription/NCIS

[b]Calculation of busulfan infusion solution: [(busulfan dose (mg) divided by 6) x 10] *[to the nearest 10ml]* NaCl 0.9%. Concentration to be as close to 0.5mg/ml as possible

[c] Day +1 methotrexate to be administered at least 24 hours post completion of stem cell infusion.
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 busulfan, cyclophosphamide, mesna, 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.

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 emesis			Prevention of delayed emesis			Comments
Drug	**Dose**	**Admin day**	**Drug**	**Dose**	**Admin day**	
Ondansetron	8mg PO/IV TDS	-7 to -1	Dexamethasone	8mg PO	0,+1, +2	Exclude aprepitant due to cyclophosphamide/ aprepitant interaction
Dexamethasone	12mg PO	-2, -1				

Cyclophosphamide hydration and diuresis:

- Pre stem cell infusion: Start pre-hydration at 6.00 am on Day -2
  - 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

Busulfan conditioning seizure prophylaxis:

- Phenytoin 600mg STAT orally at midnight the night before busulfan treatment, then 300mg once daily PO on Day -7 to Day -3

OTHER SUPPORTIVE CARE:

Table 2: Recommended SJH regimen specific supportive care

GvHD prophylaxis: Refer to signed off BMT assessment form for confirmed **choice and target level** of immunosuppression	**Ciclosporin** • Ciclosporin 5mg/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: 100-150microgram/L	**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 nanogram/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 patient 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) 10ml 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:	**Methotrexate is included as GvHD prophylaxis. Folinic acid should not be administered on the same days as methotrexate.** The first dose of folinic acid must be administered at a minimum of 24 hours post completion of methotrexate. Prescribe as outlined below: • Folinic acid 15mg once daily IV on days **+2,+4,+5 and +7 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 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 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

Hepatic veno occlusive disease (VOD):

- Defibrotide may be prescribed for the treatment of hepatic veno-occlusive disease (VOD) in consultation with the haematology consultant
- Dosing of intravenous Defibrotide :
  - The recommended dose is 6.25mg/kg IV every 6 hours (25mg/kg/day)
    - Calculate the total daily dose. Divide by 200 to calculate the total number of vials needed and split the dose such that the minimum amount of wastage can be achieved.
  - Defibrotide should be administered for a minimum of 21 days and continued until the signs and symptoms of VOD resolve.
    - IV infusion is given over 2 hours (maximum concentration 400mg/100ml NaCl 0.9%)

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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13. Methotrexate 1g/10ml Summary of Product Characteristics. Accessed November 2020. Available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-206-006_19052021104201.pdf

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.