Fludarabine/Busulfan/ATG Grafalon® – RIC –SIB

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Reduced intensity conditioning for sibling donor allogeneic stem cell transplant in patients with myeloid disorders.	C92	00636a	Hospital

TREATMENT:

Conditioning chemotherapy is administered over **9 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
-9,-8,-7,-6,-5,-4	Fludarabine[a]	30mg/m^2	IV infusion	100ml sodium chloride 0.9% over 30 minutes
-5,-4,-3 (10.30)*	Busulfan[b,c]	0.8mg/kg	IV infusion	(See note[d]) ml sodium chloride 0.9% over 2 hours
-5,-4,-3 (16.30)*	Busulfan[b,c]	0.8mg/kg	IV infusion	(See note[d]) ml sodium chloride 0.9% over 2 hours
-5,-4 (22.30)*	Busulfan[b,c]	0.8mg/kg	IV infusion	(See note[d]) ml sodium chloride 0.9% over 2 hours
-4,-3 (04.00)*	Busulfan[b,c]	0.8mg/kg	IV infusion	(See note[d]) ml sodium chloride 0.9% over 2 hours
NB: IV busulfan expires after 15 hours, infusion must begin at time specified				
- 3	[e,f,g] ATG Grafalon®	10mg/kg	IV infusion	(See note[h]) ml sodium chloride 0.9% over 12 hours
-2,-1	[e,f,g] ATG Grafalon®	10mg/kg	IV infusion	(See note[h]) ml of sodium chloride 0.9% over 10 hours
0	Stem cell infusion			
+1,+3,+6 (At least 24 hours post end of stem cell infusion)	Methotrexate[i]	10mg/m^2	IV infusion	50mls of sodium chloride 0.9% over 10 minutes

Dose rounding:
Fludarabine doses ≤50mg to the nearest 2.5mg and doses >50mg to the nearest 5mg
Busulfan to the nearest 1.2mg if <60mg, to nearest 6mg if >60mg. Oral busulfan available as 2mg and 25mg tablets.
ATG Grafalon® to the nearest 20mg
Methotrexate to the nearest 2.5mg

[a]All patients who have received fludarabine should receive irradiated blood products (lifetime recommendation).

[b]IV busulfan may be replaced with oral busulfan at the discretion of the haematology consultant. An oral dose of 1mg/kg is equivalent to the 0.8mg/kg IV dose **The dosing schedule for oral busulfan is 06:00, 12:00, 18:00, 23:59**
[c]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
[d]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.

[e]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.
[f]If an infusion reaction occurs during the administration of ATG Grafalon®, 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.
[g] Platelets should be >50x10^9/L pre day 1 ATG Grafalon® treatment. If the patient has no reaction to ATG Grafalon®, platelets can be maintained at >30x10^9/L for the remaining days of ATG Grafalon® administration. Platelets should be maintained at >50x10^9/L in the setting of clinically symptomatic bleeding.
[h]Each ml of ATG Grafalon® should be diluted with 6ml of sodium chloride 0.9% in accordance with SPC. Pharmacy to complete volume.

[i]Day +1 methotrexate should be administered at least 24 hours after the stem cells have infused. 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 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 time

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to fludarabine, busulfan, 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.

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 Anti-emetics

Prevention of acute emesis			Prevention of delayed emesis			Comments
Drug	**Dose**	**Admin day**	**Drug**	**Dose**	**Admin day**	No additional dexamethasone is required due to steroid cover with ATG Grafalon® supportive medication
Ondansetron	8mg PO/IV TDS	-5, -4, -3	No delayed cover required	N/A	N/A	

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 and equivalent IV alternative starting on Day 0 and continuing for 5 days
- Taper to zero over next 5 days to prevent serum sickness

Busulfan conditioning seizure prophylaxis:

- Phenytoin 600mg STAT orally at midnight the night before busulfan treatment, then 300mg once daily PO on day -5 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/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 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	<u>First line therapy</u> • Co-trimoxazole 960mg BD Mon/Wed/Fri PO • Commence only on engraftment when ANC > 1.0x10^9/L if appropriate <u>Second line therapy (if allergic to co-trimoxazole or contraindicated):</u> *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)
Gastro protection:	• 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 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:

1. Kröger N et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Blood. 2009;114:5264-5270
2. Improved survival with ursodeoxycholic acid prophylaxis in allogenic stem cell transplantation: Long-term follow-up of a randomised study. Biology of Blood and Marrow Transplantation 2014; 20(1):135-138. Available at https://pubmed.ncbi.nlm.nih.gov/24141008/
3. Veno-occlusive disease/sinusoidal obstruction syndrome after haematopoietic stem cell transplantation: Middle East/North Africa regional consensus on prevention, diagnosis and management. Bone Marrow Transplantation 2017 Apr;52(4):588-591. Available at https://pubmed.ncbi.nlm.nih.gov/27892944/
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. 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
7. Krens S D, Lassche,Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019; 20:e201-08. https://doi.org/10.1016/S1470-2045(19)30145-7

8. Fludara® summary of product characteristics accessed Oct 2020 available at https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0611-004-001_11112019115658.pdf
9. Busilvex ® Summary of Product Characteristics Accessed Oct 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/busilvex-epar-product-information_en.pdf
10. Grafalon ATG ® summary of product characteristics accessed Oct 2020 Available at : https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1015-001-001_19032020152832.pdf
11. Methotrexate 1g/10ml Summary of Product Characteristics. Accessed October 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

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.