Carmustine/Etoposide/Cytarabine/Melphalan/Alemtuzumab RIC-SIB/MUD

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Reduced intensity conditioning for sibling or matched unrelated allogeneic stem cell transplantation in Hodgkins and Non-Hodgkins Lymphoma	C81 C85	00638a	Hospital

TREATMENT:

Conditioning chemotherapy is administered over **6 days**. Stem cells are infused on **day 0**.

Facilities to treat anaphylaxis MUST be present when the conditioning therapy and stem cells are administered.

Day (time)	Drug	Dose	Route	Diluent & Rate
-6	Carmustine[a,b,c]	300mg/m^2	IV infusion	1000ml glucose 5% over 1 hour
-5,-4,-3,-2 **(AM dose)**	Cytarabine	200mg/m^2	IV infusion	100ml sodium chloride 0.9% over 30 mins
-5,-4,-3,-2	Etoposide	100mg/m^2	IV infusion	1000ml sodium chloride 0.9% over 2 hours
-5,-4,-3,-2 **(Commence immediately after first etoposide dose has been administered)**	Etoposide	100mg/m^2	IV infusion	1000ml sodium chloride 0.9% over 2 hours
-5	Alemtuzumab	10mg	IV infusion	100ml sodium chloride 0.9% over (see below)[d]
-4,-3,-2,-1	Alemtuzumab	10mg	IV infusion	100ml sodium chloride 0.9% over 4 hours[e]
-5,-4,-3,-2 **(PM dose - 12 hours post start of AM dose)**	Cytarabine	200mg/m^2	IV infusion	100ml sodium chloride 0.9% over 30 mins
-1	Melphalan[f,g]	140mg/m^2	IV push	Into side arm of fast flowing sodium chloride 0.9% infusion over 30 mins
0	Stem Cell Infusion			
Start +6 **(until ANC > 1.0x10^9/L for two consecutive days)**	Filgrastim (GCSF)	300 mcg	S/C	n/a

Dose rounding
Carmustine doses to the nearest 3.3mg
Etoposide to the nearest 4mg if ≤200mg and nearest 20mg if >200mg
Cytarabine to the nearest 20mg
Melphalan to the nearest 5mg

[a]If carmustine is unavailable, lomustine 200mg/m^2 PO day -6 can be substituted. Lomustine is rounded to the nearest 40mg capsule and is contraindicated in patients with coeliac disease/wheat allergy

[b]When reconstituted carmustine has a very short expiry time. **(Refer to local policy for guidance on stability and shelf life to co-ordinate administration with pharmacy compounding)**

[c]Carmustine intravenous solution is unstable in polyvinyl chloride container. The carmustine solution should be administered from PVC free containers only.

[d]10ml/hr for first hour, 20ml/hr for second and third hours, 30ml/hr for subsequent hours

[e]4 hour infusion applicable if tolerated on day -5

[f]When reconstituted melphalan has a very short expiry time. **(Refer to local policy for guidance on stability and shelf life to co-ordinate administration with pharmacy compounding)**

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to carmustine, etoposide, cytarabine, melphalan, alemtuzumab 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 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

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

SUPPORTIVE CARE:

Antiemetics:

Table 1: Recommended SJH regimen specific anti-emetics

Prevention of acute nausea and vomiting			Prevention of delayed nausea and vomiting			Comment
Drug	**Dose**	**Admin Day**	**Drug**	**Dose**	**Admin Day**	
Dexamethasone	6mg PO	-1	Dexamethasone	4mg PO	0, +1, +2	Dexamethasone with melphalan only
Ondansetron	8mg PO/IV[a] TDS	-6 to -1	Aprepitant	80mg PO	0, +1	
Aprepitant	125mg PO	-1				
[a]May be administered orally						

Alemtuzumab Pre-medication:

Prior to alemtuzumab therapy (i.e. 60 minutes pre-therapy), the following should be administered:

- Paracetamol 1g PO
- Chlorphenamine 10mg IV
- Hydrocortisone 100mg IV

Other pre-medications:

- **Melphalan hydration:** Sodium chloride 0.9% must be given at a rate of 125ml/m^2/hour for two hours pre melphalan and for 6 hours post melphalan

Other Supportive Care:

Table 2: Other Supportive Medication

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: 100-150micrograms/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 nanograms/ml
GvHD and VOD prophylaxis	• Ursodeoxycholic acid 250mg TDS PO • Continue until day +90	

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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 <$0.5x10^9$/L or if patient on high dose steroids: • Liposomal amphotericin 1mg/kg once daily IV Mon/Wed/Fri **or** • Caspofungin 70mg 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 followed by 50mg once daily IV thereafter if <80kg

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

PJP 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): *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)
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 is 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

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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 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. • 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.

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

REFERENCES:

1. Pilot of Allogeneic Immunotherapy in Refractory Disease (PAIReD). Phase II study of reduced intensity allogeneic transplantation for refractory Hodgkin lymphoma. Protocol version 2.0 dated 7th May 2010. Trial Sponsor: University College London. Chief Investigator: Dr Karl Peggs. Protocol available upon request from paired@ctc.ucl.ac.uk
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. 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
5. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
6. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
7. 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
8. Carmustine Summary of Product Characteristics Accessed: Nov 2020. Last updated: 12/11/2018 Available at: https://www.ema.europa.eu/en/documents/product-information/carmustine-obvius-epar-product-information_en.pdf
9. Etoposide Summary of Product Characteristics Last updated: 18/11/16. Accessed Jul 2019. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2059-036-001_29072019103821.pdf
10. Cytarabine Summary of Product Characteristics. Last updated: 28/09/18. Accessed Nov 2020. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA0822-200-002_28092018160744.pdf
11. Alkeran Summary of Product Characteristics Last updated: 16/04/18 Accessed Jul 2019. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1691-004-001_14112019130102.pdf
12. Lemtrada 12 mg concentrate for solution for infusion. Summary of Product characteristics. Accessed Nov 2020. Available at: https://www.ema.europa.eu/en/documents/product-information/lemtrada-epar-product-information_en.pdf

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens

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.

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient's care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE's terms of use available at http://www.hse.ie/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoregimens