BCNU Thiotepa (high dose)

Summary of Schedule

Date:

	DAY								
DRUG	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**	**+1**
Admission	*								
Carmustine (BCNU) *Chemotherapy*		*							
Thiotepa *Chemotherapy*			**	**					
Stem cell infusion								*	
Pentamidine IV * *To prevent a specific pneumonia called PCP*									*
Dexamethasone (D) Ondansetron (O) Aprepitant (A) *Different types of anti-sickness*		D O A	D O A	D O A	O	O	O	O	

Indication

Consolidation treatment for primary CNS lymphoma first or second line
Consolidation treatment for secondary CNS lymphoma first or second line

Treatment Intent

Curative

Pre-Assessment

- Ensure pre-transplant 'work-up' Investigation form (B.3.10d) is complete and results checked by Haematology SpR and recorded in patient record.
- Ensure patient has a triple lumen central line in situ and is patent.
- High risk of early severe mucositis, consider early NG feeding/TPN.
- Haematology SpR to complete electronic BMT front sheet. Administrator for BMT Nurses to distribute and file in patient record.
- Prescribe chemotherapy, stem cells/bone marrow infusion and supportive treatment 10 days before admission.
- Send NHSBT form ‘Request for Issue of Cyropreserved Products’ to NHSBT at least 7 days before planned infusion date and ensure copy of confirmation is placed in the patient’s record.
- Perform a urine pregnancy test on Day -*7*, in all women of child bearing potential of age. Document results in patient record
- Ensure the patient receives irradiated bloods products from start of conditioning. See ‘Guidelines for the Use of Blood Components in Adult Haematology’ for further details and individual requirements/duration post autograft. Ensure irradiation card is attached to the patient’s notes and copy given to the patient
- Treatment should be agreed in the relevant MDT

Chemotherapy and IV Fluids

Encourage 3L oral fluids daily, give **IV** if oral intake insufficient.

Day -6		
T = 0 hr	**CARMUSTINE (BCNU)**	**400 mg/m2** in 500 mL glucose 5% **IV infusion over 2 hours**
T = +2 hrs	**Hydration**	2000mL sodium chloride 0.9% **IV infusion over 24 hours** to be started immediately after BCNU infusion.
Day -5 & -4		
T = 0 hr	**THIOTEPA**	**5mg/kg** in 250-1000mL* sodium chloride 0.9% via **IV infusion over 2-4 hours** (final concentration 0.5-1mg/mL) Administer via infusion set equipped with a 0.2 micron in-line filter
T = 0 hr	**Hydration**	3000mL sodium chloride 0.9% **IV** infusion over 24 hours to be started with the first thiotepa infusion, run concurrently with the chemotherapy.
T = +12 hrs	**THIOTEPA**	**5mg/kg** in 250-1000mL* sodium chloride 0.9% via **IV infusion over 2-4 hours** (final concentration 0.5-1mg/mL) Administer via infusion set equipped with a 0.2 micron in-line filter
Day 0		
07:00	**Hydration**	1000 mL sodium chloride 0.9% **IV infusion over 6 hours**
Approx 13:00	**Stem cell re-infusion**	Give hydrocortisone 100 mg **IV**, chlorphenamine 10 mg **IV** and 15 minutes before infusion.
Day +1	**Pentamidine**	4mg/kg (max 300mg) in 100ml sodium chloride 0.9% **IV infusion over 1 hour**. Intravenous pentamidine for PCP prophylaxis should be considered for all patients during conditioning chemotherapy. Day +1 is the most logistically feasible time. If this falls at a weekend defer to the next working day.
Day +5	**GCSF (filgrastim)**	Daily subcutaneous injection. Dosing as per local policy until stable engraftment. Substitutions for long-acting granulocyte stimulating colony factors such as peg-filgrastim **are not permitted**.
*Dose 140mg to 260mg in 250ml, 270mg to 560mg in 500ml, doses greater than or equal to 570mg in 1000ml. If dose in 1000mL sodium chloride 0.9% administer over 4 hours		

NB: For obese patients refer to NSSG Guideline – "Guidelines on Chemotherapy Dosing in Obese Adult Patients Undergoing Stem-cell / Bone Marrow transplant".

Refer to nursing care plans:
Administration of chemotherapy
Pentamidine
Stem cell re-infusion

Dose Modifications

Discuss all modifications with treating consultant.

Thiotepa

Consider **omitting the second thiotepa dose** at 12 hours (resulting in 50% dose) on days -5 and -4 for patients **with significant co-morbidity.**

Renal impairment – Limited information available, dose modification not routinely advised.

Hepatic impairment – Limited information available, majority metabolized via liver. Clinical decision in severe impairment.

Carmustine

Carmustine can be associated with induced interstitial pneumonitis in the transplant setting. **Consider omitting BCNU if lung function tests < 75% predicted or heavy smoker**. Exercise caution in patients with prior mediastinal irradiation or bleomycin use.

Renal Impairment – limited data available, clinical decision guided by table below

Creatinine clearance (mL/min)	Carmustine dose
45 - 60	80%
30 - 45	75%
<30	Clinical decision

Hepatic impairment – dose modification not recommended.

Investigations

Daily	Full blood count (FBC), creatinine, urea & electrolytes (U&Es), weight, urinalysis
Alternate days	Liver function tests (LFTs)
Mon/Thurs	Coagulation screen, calcium, magnesium, phosphate
Mon/Fri	Group and save (G&S)
Other	Chest X-ray on admission then weekly and as clinically indicated Other specimens for virology as clinically indicated

Concurrent Medication

Norethisterone	In menstruating women only, 5 - 10 mg PO/TDS from day 0 until platelets > 50 x 10^9/L
Fluconazole	50 mg PO/OD from day 0 until neutrophils > 1.0 x 10^9/L (or longer if patient on steroids). Refer to **NSSG Antifungal protocol**.
PPI (choice can be guided by local formulary)	Omeprazole 20mg PO/OD (or local choice of PPI) from start of conditioning until platelet count > 50 x 10^9/L.
Aciclovir	200 mg PO/TDS (or 250 mg TDS/IV) from day 0 until day +90.
G-CSF (filgrastim)	Once daily subcutaneous injection, dose as per local policy, from day +5 until stable engraftment. Substitutions for long-acting granulocyte stimulating colony factors such as peg-filgrastim **are not permitted**.
Pentamidine	4mg/kg/day (max dose 300mg) IV on day +1 and day +30, unless started on co-trimoxazole.

Anti-emetics

Regular antiemetics*	
5HT3 antagonist	Days -6 to 0 i.e. Ondansetron 8mg PO/IV/BD
Dexamethasone	Days -6 to -4: Dexamethasone 8mg PO/IV/OD on day -6, then dexamethasone 4mg PO/OD on days -5 to -4.
NK1 inhibitor	Days -6 to -4 i.e. Aprepitant 125mg OD on day -6, then 80mg on days -5 and -4
Consider olanzapine 5 - 10mg PO/OD days -6 to -4 as per local formulary	
When required antiemetics* from the start of conditioning for rescue antiemetic	
5HT3 antagonist	Ondansetron 8mg PO/IV prn, maximum 32mg in 24hours
Cyclizine	50mg PO/IV/TDS prn
* Review antiemetic control and optimise in case of breakthrough N&V	

Extravasation risk
Carmustine - vesicant
Thiotepa - neutral

For management of extravasation refer to **TVCA Extravasation Policy.**
(https://thamesvalleycanceralliance.nhs.uk/healthcare-professionals/chemotherapy/)

Medications on Discharge (TTOS)

Norethisterone	In menstruating women only, 5 - 10 mg PO/TDS from day 0 until platelets > 50 x 10^9/L
Fluconazole	50 mg PO/OD stop when neutrophils > 1.0 x 10^9/L, continue if patient remains at risk of on-going immunosuppression e.g., on steroids.
Co-trimoxazole	**Start when neutrophils > 1.0 x 10^9/L -** 960 mg daily Mon, Wed, Fri until day +120 If allergic to co-trimoxazole, pentamidine 4mg/kg (max 300mg) IV infusion 4-weekly.
Aciclovir	200 mg PO/TDS until day +90.
PPI (choice can be guided by local formulary)	Omeprazole 20mg OD (or local choice of PPI). Stop when platelet count >50 x 10^9/L unless clinically indicated to continue.

Treatment Related Mortality: 2 - 5%

References:

1. Illerhaus G. *et al* 'High dose chemotherapy and autologous stem cell transplantation without consolidation radiotherapy as first-line treatment for primary lymphoma of the central nervous system.' Haematologica (2008) **93:** 147-148
2. Illerhaus G. *et al* 'High-dose chemotherapy with autologous stem cell transplantation and hyperfractionated radiotherapy as first-line treatment of primary CNS lymphoma.' JCO (2006) **24:** 3865-3870
3. UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)
4. UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)
5. IELSG 32: Randomized Phase II trial on Primary Chemotherapy with High-Dose Methotrexate and High-Dose Cytarabine with or without Thiotep, and with or without Rituximab, followed by Brain Irradiation vs. High-Dose Chemotherapy supported by Autologous Stem Cells Transplantation for Immunocompetent patients with newly diagnosed Primary CNS Lymphoma. EudraCT number 2009-012432-32

Author(s): Dr Graham Collins

Audit
These processes are subject to the OxBMT audit programme

Circulation
NSSG Haematology Website

Review

Name	Revision	Date	Version	Review date
Graham Collins, Consultant	Auto Protocol Review Day	Aug 2017	2.4	Aug 2019
Jaimal Kothari, Consultant Nadjoua Maouche, Haematology Pharmacist Cristina Ovas, Quality and Data Manager	No changes, Revised anti-emetic regime BMT document formatting	June 2019	2.5	June 2021
Kirsten Rendall, BMT Specialist Nurse Donna Constantine, Advanced Cancer Pharmacist Toby Eyre, Consultant	Amendments to chemo timings + document formatting. Clarification to recc. dose adjustments. Addition of nursing care plan	April 2023		

CARE PLAN ON NEXT PAGE

Nursing Care Plan

Ensure flush volumes are included in rate and volume calculations, i.e. drug and flush should be completed within prescribed administration time.

Carmustine (BCNU) – a cell-cycle phase nonspecific antineoplastic alkylating agent which prevents DNA replication and DNA transcription of the cancer cells.
Side effects: headache, facial flushing (during infusion), dizziness, nausea & vomiting, bone marrow depression
Extravasation risk: vesicant

Day -6

- Encourage 3L oral fluids daily
- Give carmustine in the morning, between 0900-1100
- Prime giving set with 5% glucose as carmustine is manufactured in glucose for stability
- Administer over 2 hours as prescribed
- Flush with 5% glucose when infusion complete
- Immediately after completion of carmustine, commence IV pre-hydration. This needs to run continuously for 24 hours before thiotepa starts on D-5 (2 x 1L bags Sodium Chloride 0.9% which run for 12 hours each).

Thiotepa – an alkylating agent which is cell cycle non-specific. Thiotepa causes cross-linkage between two strands of DNA, interfering with DNA, RNA and protein synthesis.
Side effects: nausea & vomiting, mouth sores, skin rash, diarrhoea, bone marrow depression, reduced fertility.
Extravasation risk: neutral.

Day -5 & -4

- Check expiry date and times of all available bags of thiotepa carefully as it has a short expiry time.
- Check the volume of delivered thiotepa as this will determine the speed of administration:
    - 140-260mg will be in 250mls and should be given over 2 hours
    - 270-560mg will be in 500mls and should be given over 2 hours
    - ≥570mg will be in 1000mls and should be given over 4 hours
- Check ARIA prescription carefully as some patients will only have OD dosing, rather than BD
- Once hydration from D -6 is complete, administer thiotepa via infusion set equipped with a **0.2 micron filter**
- Simultaneously commence IV hydration as per ARIA prescription. This should run concurrently with the thiotepa and will continue for 24 hours (3 x 1L bag Sodium Chloride 0.9% which run for 8 hours each).
- If patient is on BD dosing, administer second dose of thiotepa 12 hours after morning dose. IV hydration will run concurrently and continuously. IV hydration should run until the following morning.
- Closely monitor patient for signs of fluid overload as high volume of oral and IV hydration given over consecutive days.

D -3, -2 & -1

- Rest days

Stem cell infusion of frozen cells, potential complications: Allergic reaction, fluid overload, hyperosmolarity, infusion of micro-aggregates, pulmonary oedema, nausea, vomiting, diarrhoea, abdominal pain, and facial flushing, headache, blurred vision, altered taste and smell due to DMSO.

Day 0

- **0700**: Administer sodium chloride 0.9% 1 litre over 6 hours
- **0800**: Liaise with Stem Cell Services for timing of cell arrival
- **1245**: Administer pre-medications: chlorphenamine, hydrocortisone + antiemetics as prescribed a minimum of 15 minutes prior to stem cell reinfusion
- Ensure O2, suction, and call bell are checked, and anaphylaxis kit is in patient room
- **1300**: Peripheral Blood Stem Cell Infusion:
- Record baseline observations
- Positively identify the patient ID, against each bag of cells and on NHSBT Form 5071 (EPR under 'BMT Coordination')
- Check cells to ensure no clumping or bag damage
- Take great care when spiking each bag, to prevent inappropriate puncturing. See Cell Management policy NSSG> BMT> Clinical Management> B.2.30 if bag is accidentally punctured
- Each bag of cells must be infused within 15 mins of thawing. The cells may be infused through a:
  Central line using an **appropriate** infusion pump and associated double spike giving set (*filter size equivalent) side-armed with Sodium Chloride 0.9%.
  OR
  Peripheral cannula using a blood administration giving set* side-armed with Sodium Chloride 0.9% using a Y connector, and gravity feed
- Monitor patient closely and observe for any signs of reaction, fluid overload and/or respiratory compromise.
- Record: lot numbers of giving sets and saline, and volume of cells including start and completion time for each bag, on NHSBT form 'Summary of products issued for transplant'
- On completion of cells, continue flushing the IV line with saline until it runs clear
- Ensure a copy of the NHSBT form 'Record of issue and infusion' and 'Summary of products issued for transplant' is scanned/ filed in patient EPR
- Ensure completion of NHSBT adverse event form is completed and returned to Haematology Ward Clerk who will forward to NHSBT/SCI

Day +1

Pentamidine isethionate is an antimicrobial medication primarily given for prevention and treatment of Pneumocystis pneumonia (PCP), a severe interstitial pneumonia often seen in patients that are immunocompromised.

Side Effects: May cause hypotension and arrhythmias if electrolytes have not been corrected; dizziness; hypoglycaemia, nausea + vomiting

- Bloods pre administration; U& E's, creatinine, and FBC.
- Administer any replacements necessary prior to infusion.
- (Refer to guidelines for management of hypomagnesaemia in adult clinical haematology on NSSG> Clinical Haematology OUH> Haematology Day Treatment Unit).
- Ensure anti-emetic cover as per protocol
- Perform ECG immediately before administration. Check with the SHO or Registrar to ensure they are happy for you to commence infusion. ECG should then be repeated and reviewed 30 minutes into the infusion and immediately after first dose. (This only needs to be done if first dose of pentamidine).
- Before administration, check blood sugar is within normal range
- Check baseline observations, then 30 minutes into infusion and 5 minutes after completion of infusion.
- Ensure the patient is lying down or sitting in a chair whilst the Pentamidine is being infused
- Wear gloves, and apron whilst hanging the bag.
- Administer over 1 hour.
- Check blood sugar 60 minutes post-infusion.

NB. If the patient has experienced a previous reaction, you may need to consider slowing subsequent infusions. The patient may also require a pre-med of paracetamol or anti-emetic. In these cases you may advise the patient to eat or drink something sweet during the infusion.

Author(s) Nursing Care Plan: Kirsten Rendall, Autologous BMT Coordinator

Authorised by: Denise Wareham, BMT Senior Specialist Nurse

Audit: These processes are subject to OxBMT audit programme

Circulation: NSSG Haematology Website, patient notes

Review

	Revision	**Date**	**Version**	**Review date**
Kirsten Rendall Auto BMT Coordinator, Denise Wareham BMT Senior Specialist Nurse	Revised nursing care plan and added as an integrated part of the clinical protocol	Feb 2022	1.0	Align with clinical protocol
Donna Constantine, Haematology Pharmacist, Kirsten Rendall, BMT,	Some clarification around renal/hepatic dose adjustments for	April 2023	2.6	April 2025

Senior Specialist Nurse	thiotepa and hepatic impairment and reviewed the nursing care plan			