

Systemic Anti Cancer Therapy Protocol

MATRIX PRIMARY CNS LYMPHOMA

PROTOCOL REF:
(Version No. 2.1)

Approved for use in:

- CNS Lymphoma

Blueteq not required

Dosage:

Drug	Dose	Route	Frequency
Rituximab	375mg/m ²	IV infusion	Day 1
Methotrexate	3500mg/m ²	IV infusion	Day 2 (split into 500mg/m ² over 15 minutes and then 3000mg/m ² over 3 hours)
Cytarabine	2000mg/m ²	IV infusion	BD on days 3 and 4.
Thiotepa	30mg/m ²	IV infusion	Day 5
Rituximab	375mg/m ²	IV infusion	Day 6

Maximum of 4 cycles (21 day cycles)

Administration (+/- Counselling Points):

- **Co-trimoxazole and PPIs must be stopped at least 2 days prior to treatment**
- Piperacillin/Tazobactam (Tazocin®) should be avoided and meropenem used as first line treatment for febrile neutropenia following methotrexate infusion until methotrexate has cleared (level <0.1micromol/L)
- Due to the long retention time of rituximab in B cell depleted patients, women of childbearing potential should use effective contraceptive methods during and for 12 months following treatment with rituximab.

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- The hydration fluids on day 3 **MUST** start at least 6 hours prior to the methotrexate infusion.
- The patient's urine pH **MUST** be >7 before the methotrexate infusion is started.
- If urinary pH <7 during methotrexate infusion then additional sodium bicarbonate 8.4% 50mL can be infused separately by slow IV infusion (to be prescribed prn in Meditech).
- The second methotrexate infusion **MUST** start immediately after the loading dose.
- The blood sample needs to be sent to Alder Hey hospital in a taxi and then the lab at Alder Hey need to be rung for the result which should be documented in the medical notes.
- Folinic acid (calcium folinate) should be started 24 hours after the **start** of the methotrexate infusion
- The first methotrexate level should be taken 48 hours after the **start** of the methotrexate infusion. The methotrexate level should then be repeated daily until it is <0.1micromol/L at which point folinic acid rescue can stop.
- The dose of folinic acid (calcium folinate) may need to be modified 48 hours after the start of the methotrexate infusion in response to methotrexate levels (see High Dose Methotrexate Overview Protocol)
- If the serum creatinine increases by more than 25% from baseline then the folinic acid rescue should be escalated even before methotrexate level is known – seek urgent consultant advice.

Emetogenic risk

Severely emetogenic

Supportive treatments:

Rituximab pre-infusion medicines:

- Paracetamol PO 1g
- Chlorphenamine IV bolus 10mg
- Hydrocortisone sodium succinate IV bolus 100mg

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High dose methotrexate pre-infusion medicines:

- Hydration fluids to start at least 6 hours before methotrexate
- Sodium bicarbonate 1g PO four times daily from 24 hours pre-methotrexate
- Sodium bicarbonate 8.4% IV 50mL slow IV bolus prn (to be used if urinary pH <7)

Supportive medicines:

- Allopurinol oral 100mg or 300mg once daily (depending on renal function) for first cycle
- Aciclovir 400mg oral twice daily
- Famotidine 20mg twice daily (if on existing PPI therapy, not needed routinely)
- Filgrastim S/C 30 or 48 million units OD from day 9 for 7 days (30million units if <70kgs and 48 million units >70kgs) when NOT used for priming. See below for information when used for mobilisation prior to haematopoietic stem cell harvesting
- Fluconazole oral 50mg once daily
- Folinic acid IV 60mg every 6 hours to start 24 hours after the start of methotrexate infusion. See administration advice for further information.
- Ondansetron oral 8mg BD (IV on days 2 to 5)
- Pentamidine NEB 300mg every 28 days OR atovaquone liquid oral 750mg BD
- Prednisolone 0.5% eye drops 1 drop into both eyes four times daily starting day 3 for 10 days

Suspend co-trimoxazole and routine folic acid until methotrexate level <0.1micromol/L

Extravasation risk:

Rituximab: non-vesicant

Methotrexate: non-vesicant

Cytarabine: non-vesicant

Thiothepa: non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

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Dosing in renal and hepatic impairment:

A fluid space, e.g. pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. High dose methotrexate should not be given in such cases.

Methotrexate			
Renal (ml/min) – use wright equation			
>60			100% dose
40-60			50%
<40			Omit
Hepatic			
Bilirubin (micromol/L)		ALT (units/L)	Dose modification
<50	and	<180	100% dose
50-84	or	≥180	75% dose
≥85			Omit

Cytarabine	
Renal (ml/min)	
>60	100%
30-60	50%
<30	Omit
Hepatic	
If Bilirubin >34micromol/L give 50% initially and escalate for subsequent cycles in the absence of toxicity	

Thiotepa	
Renal (ml/min)	
<30	Consider 70% of original dose, increase if tolerated
Hepatic	
If Bilirubin is 1.5-3 times ULN, intensify monitoring. If >3 times ULN, not recommended	

Interactions:

Methotrexate – see High Dose Methotrexate Overview Protocol

Cytarabine

Cytarabine may reduce digoxin levels. Digoxin level monitoring is recommended.

An *in-vitro* interaction study between gentamicin and cytarabine showed a cytarabine related antagonism for the susceptibility of *K. pneumoniae* strains. In patients on cytarabine being

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treated with gentamicin for a *K.pneumoniae* infection, a lack of a prompt therapeutic response may indicate the need for re-evaluation of antibacterial therapy.

Treatment schedule:

Day	Drug	Dose	Route	Diluent and rate
1	Paracetamol	1g	PO	
	Chlorphenamine	10mg	IV	Bolus dose over 3-5 minutes.
	Hydrocortisone	100mg	IV	Bolus dose over 3-5 minutes.
	Rituximab	375mg/m ²	IV	Non-Hodgkin patients ONLY. ≤450mg 250mL sodium chloride 0.9% ≥500mg 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline.
2	IV hydration: 1L sodium chloride 0.18% / glucose 4% containing 20mmol potassium chloride and 50ml 8.4% sodium bicarbonate (bicarbonate to be added on the ward)		IV	Start infusion 6 hours prior to methotrexate infusion, run at a rate of 250ml/hr for 6 hours, then run at a rate of 125ml/hr for 3 hours 15 minutes concurrent with methotrexate infusions, then run at a rate of 250ml/hr until desired methotrexate level is achieved (<0.1micromol/l).
	Methotrexate	500mg/m ²	IV	100mL Sodium chloride 0.9% Over 15 minutes. The patient's urinary pH MUST be >7 before starting the infusion.
	Methotrexate	3000mg/m ²	IV	1000mL Sodium chloride 0.9% Over 3 hours.
3	Cytarabine (AM dose)	2000mg/m ²	IV	250mL Sodium chloride 0.9% Over 2 hours.
	Cytarabine (12 hours post AM dose)	2000mg/m ²	IV	250mL Sodium chloride 0.9% Over 2 hours.
4	Cytarabine (AM dose)	2000mg/m ²	IV	250mL Sodium chloride 0.9% Over 2 hours.
	Cytarabine (12 hours post AM dose)	2000mg/m ²	IV	250mL Sodium chloride 0.9% Over 2 hours.
5	Thiotepa	30mg/m ²	IV	100mL Sodium Chloride 0.9% over 30 minutes.
6	Paracetamol	1g	PO	
	Chlorphenamine	10mg	IV	Bolus dose over 3-5 minutes.

	Hydrocortisone	100mg	IV	Bolus dose over 3-5 minutes.
	Rituximab	375mg/m²	IV	Non-Hodgkin patients ONLY. ≤450mg 250mL sodium chloride 0.9% ≥500mg 500mL sodium chloride 0.9% Rate as per rituximab infusion guideline.
9	Filgrastim (GCSF)	<70kg: 30 million units ≥70kg: 48 million units	SC	Non-mobilisation Once daily for 7 days Mobilisation Once daily until harvesting complete.

Haematopoietic Stem Cell Mobilisation:

MATRIX day 1 should be administered on a Wednesday to facilitate apheresis starting on a Monday (day 13)

Clinical Interventions Prior to Admission

- Arrange for insertion of central venous catheter if insufficient peripheral venous access – apheresis team to assess veins if clinical suspicion that inadequate. Patient may require inpatient admission (ideally ward 4 CCC) if requiring temporary central venous access (femoral vein) and not local to CCC (within 1 hour drive) or if patient is living alone.
- Ensure adequate renal, lung and cardiac function, additional investigations may be required if clinically indicated.
- Discuss with Consultant/HPCT coordinator should any of these results fall out of normal limits
- Book apheresis session in apheresis diary from Day 13.

Patient Preparation

- Complete appropriate documentation for Stem Cell Therapeutics laboratory to request cryopreservation of HPCs.
- Ensure all blood products are irradiated for a minimum of 7 days pre-harvest.
- Explain procedures of mobilisation chemotherapy and HPC-A collection to patient and discuss potential complications.
- Offer relevant written information available.
- Obtain written informed consent from patient.

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Filgrastim

- Patients should be given the opportunity to be taught how to self-administer filgrastim. A district nurse referral for G-CSF administration should be completed if the patient is unsuitable for self-administration.

Day(s) of Harvesting – From Day 13

- A peripheral blood CD34 count should be checked.
 - if $<5 \times 10^6/L$ not for apheresis and discuss with the transplant team about return following day
 - if $5-10 \times 10^6/L$ not for apheresis but transplant team to consider plerixafor before returning the following morning
 - if $>10 \times 10^6/L$ for attempt at apheresis.
- One or more harvest procedures may be required to achieve minimal requirement of 2.5×10^6 CD34⁺/kg, usually target $4-8 \times 10^6$ CD34⁺/kg. If results are not within target range clarify with consultant in charge.

Main toxicities:

Methotrexate
Bone marrow suppression, mucositis, stomatitis, nausea, vomiting, diarrhoea, skin irritation/sensitivity, renal impairment, AKI, deranged LFTs, interstitial pneumonitis.
Rituximab
Infusion related reactions, cytokine release syndrome. Hepatitis B reactivation
Cytarabine
Bone marrow suppression, conjunctivitis
Thiotepa
Bone marrow suppression, hearing impairment, dizziness, encephalopathy, VOD, haemorrhagic cystitis, deranged LFTs.

Glucarpidase – Methotrexate reversal agent

NHS England will fund glucarpidase as a reversal agent for methotrexate (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses $>1\text{g}/\text{m}^2$)

- Who develop significant deterioration in renal function ($>1.5\text{x}$ ULN and rising, or the presence of oliguria) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg

Refer to CCC glucarpidase protocol for further information

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Investigations and treatment plan:

	Pre	All cycles day 1	All cycles Day 2	All cycles day 5	Ongoing
Informed Consent	X				
Clinical Assessment	X				As clinically indicated or at the end of treatment
SACT Assessment (including PS and toxicity assessment)	X	X			Every cycle
FBC	X	X			Every cycle
U&E & LFTs & Magnesium	X	X			Every Cycle
CrCl (Wright)	X	X			Every cycle
CT scan	X				At the end of treatment and if clinically indicated
CSF analysis	X				
Blood pressure	X	X	X		Continuous monitoring required if on Rituximab
Temperature, respiratory rate, pulse		X	X		Continuous monitoring required if on Rituximab
Methotrexate levels				X	Daily until cleared
Weight	X	X			Every cycle
Height	X				
Hepatitis B core antibody and surface antigens & Hep C & HIV 1+2	X				
Blood glucose	X				Repeat if clinically indicated
Pregnancy test	X				If clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

Cycle one can proceed if-

ANC $\geq 2.0 \times 10^9/L$	Platelets $\geq 100 \times 10^9/L$
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Subsequent cycles can proceed if-

ANC $\geq 1.5 \times 10^9/L$	Platelets $\geq 90 \times 10^9/L$
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Note therapy can proceed if values are below these levels if cytopenias known to be secondary to disease.

If counts are below above values then MATRIX should be delayed for a maximum 2 weeks (thereafter chemo will need to be discontinued).

If nadir (following previous course) neutrophils $<0.5 \times 10^9/L$ **or** platelets $<25 \times 10^9/L$ - reduce cytarabine dose by 25% (by omitting the 4th dose). If nadir platelets $<25 \times 10^9/L$ - reduce thiotepa dose by 25%.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Age related dose reductions:

Consider reducing the dose of cytarabine by 25% in patients >65 years old (by omitting the 4th dose) and reducing the thiopeta dose by 25%.

Non- Haematological toxicity:

See section entitled 'Dosing in Renal and Hepatic Impairment'

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Infusion Related Reactions:

Non-Haematological toxicities:	
Rituximab	
<p>Infusion-related Reactions</p>	<p>Severe infusion-related reactions with fatal outcome can have an onset ranging within 30 minutes to 2 hours after starting the first rituximab infusion. They can be characterised by pulmonary events and in some cases included rapid tumour lysis and features of tumour lysis syndrome (TLS) in addition to fever, chills, rigors, hypotension, urticaria, and angioedema.</p> <p>Severe cytokine release syndrome may occur. Monitor patients closely. Patients who develop evidence of severe reactions, especially severe dyspnea, bronchospasm or hypoxia should have infusion interrupted immediately. The patient should then be evaluated for evidence of TLS including appropriate laboratory tests and, for pulmonary infiltration, with a chest x-ray. The infusion should not be restarted until complete resolution of all symptoms, and normalisation of laboratory values and chest x-ray findings. At this time, the infusion can be initially resumed at not more than one-half the previous rate. If the same adverse reaction occurs for a second time, the decision to stop the treatment should be seriously considered on a case-by-case basis.</p> <p>Anaphylactic and other hypersensitivity reactions may occur. In contrast to cytokine release syndrome, true hypersensitivity reactions typically occur within minutes after starting infusion.</p> <p>Mild or moderate infusion-related reactions usually respond to a reduction in the rate of infusion. The infusion rate may be increased upon improvement of symptoms</p>

References:

1. <https://www.medicines.org.uk/emc> rituximab (accessed April 2020)
2. <https://www.medicines.org.uk/emc> methotrexate (accessed April 2020)
3. <https://www.medicines.org.uk/emc> cytarabine (accessed April 2020)
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 Oncol* 2019;20: e201–08.
5. Ferreri, A., Cwynarski, K. et al. Chemoimmunotherapy with methotrexate, cytarabine, thiotepa, and rituximab (MATRix regimen) in patients with primary CNS lymphoma: results of the first randomisation of the International Extranodal

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Lymphoma Study Group – 32 (IELSG32) phase 2 trial. Lancet Oncol 2016;3: e217-27

6. <https://bnf.nice.org.uk/drug> thiotepa (accessed April 2020)
7. Aintree Hospital NHS Trust MATRIX protocol

Circulation/Dissemination

Date added into Q-Pulse	For completion by DCM
Date document posted on the Intranet	For completion by DCM

Version History

		Author name and designation	Summary of main changes
	1.0	Mark Nelson	New protocol
March 2023	2.0	Jennifer Gibson – Principal Pharmacist HO	Transferred to new template. Removed requirement to stop methotrexate infusion after 3 hours. Harvesting information added as per lymphoma/BMT team. Rituximab IRR table added Rituximab moved from day 2 to day 6 as per Optimate. GCSF start moved from day 8 to day 9 and harvest on day 13.
Nov 2023	2.1	Jennifer Gibson – Principal Pharmacist HO	Update prednisolone eye drops to start day 3 and IV ondansetron on days 2 to 5.

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