Chemotherapy Protocol

DRUG REGIMEN
MATRIX (Methotrexate, Cytarabine, Thiotepa, Rituximab)

Indication for use
Primary CNS lymphoma (PCNSL) - First line / selected relapses to aim for complete remission and for patient to also receive consolidation therapy. Radical intent.

Regimen

Rituximab 375mg/m^2 iv in 500mls NaCl 0.9% day 1 and 6 (see Rituximab infusion protocol)

Methotrexate 3.5g/m^2 iv day 7 (0.5g/m^2 iv in 100mls NaCl 0.9% over 15 mins then 3g/m^2 iv in 500mls NaCl 0.9% over 3 hours)
Calcium folinate rescue start 24 hours after start of methotrexate infusion

Cytarabine 2g/m^2 iv in 1000mls NaCl 0.9% over 1 hour BD (12 hourly) on days 8 and 9 (total 4 doses)

Thiotepa 30mg/m^2 iv in 50-100mls NaCl 0.9% over 30 minutes on day 10

21 day cycle x 4 cycles.

Day 1 and 6 Rituximab can be given on the Day Case Unit in the Rosemere Centre. Days 7-10 are given as an inpatient on the Ribblesdale ward only. The Patient should be admitted to the ward on day 6 ready to commence treatment at 6am on day 7.

Day 6 fluids – ensure a fluid intake of 4 litres in the 24 hours prior to initiating the methotrexate schedule below. Give a stat dose of 3g sodium bicarbonate PO in the evening of day 6.

Methotrexate Schedule

Day	Drug	Dose	Fluid	Route	Duration
7	Pre hydration Start 6am		1000 ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	4 hours
Check urine PH > 7 before proceeding to methotrexate					
7 10 AM	Methotrexate	500mg/m^2	100ml 0.9% sodium chloride	IV	15 min
7 11 AM	Methotrexate	3000mg/m^2	500 ml 0.9% sodium chloride	IV	3 hours
7 10 AM	**Concurrent fluids**		1000ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours
7	**Post hydration**		1000ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours
7	**Post hydration**		1000 ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours
7	**Post hydration**		1000ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours

Nb the hydration bag runs concurrently with the methotrexate infusion
Methotrexate 3000mg/m2 must stop after 3 hours even if some remaining.
Continue to ensure that urinary pH is above 7. If required give extra sodium bicarbonate (either 3.0g orally or 50ml of 8.4% IV).

Day 8 Hydration

Day	Drug	Fluid	Route	Duration
8	**Post hydration**	1000ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours
8	**Post hydration**	1000ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours
8	**Post hydration**	1000ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours
8	**Post hydration**	1000ml Glucose 4% NaCl 0.18% with 50ml 8.4% sodium bicarbonate (50mmol) and 20mmol potassium	IV	6 hours

Give the first dose of Cytarabine at the start of the day 8 hydration and then 12 hourly thereafter for 4 doses.

Strict adherence to measuring urinary pH and ensuring levels are >7.
(A urinary pH <7 (more acidic) reduces renal clearance of methotrexate and greatly increases toxicity and delays clearance).

Ensure that the fluid intake remains at 4.5 litres per 24 hours (minimum is 3 litres per 24 hours) until the methotrexate level is <$1x10^{-7}$M (0.1micromolar).
Aim for a diuresis of at least 150ml/hr - give IV Furosemide if necessary to maintain diuresis and maintain fluid balance.

Folinic Acid Rescue

Folinic acid rescue must start 24 hours after the start of the methotrexate
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Time	drug	dose	frequency	route
At 24 hours	Folinic Acid	15mg/m2	Stat	IV
24 to 48 hours	Folinic Acid	15mg/m2	Every 3 hours	IV
After 48 hours	Folinic acid	15mg/m2	Every 6 hours until methotrexate level is less than 1 x 10^{-7} M (0.1 micromolar)	IV

If not vomiting Folinic acid may be given orally after the first 2 doses

Timing of Methotrexate Levels

48 hours after start of Methotrexate
72 hours and then every 24 hours until plasma Methotrexate level less than 1x 10^{-7}M (0.1 micromolar)

Methotrexate levels are to be sent urgently to Alder Hey Hospital Biochemistry dept. Liaise with LTHTR lab and phone Alder Hey senior biochemist to check levels each day.

Dosage of Folinic Acid if MTX levels high

If **48 hour** (from start of Methotrexate infusion) Methotrexate level is >2 x 10^{-5}M (20 micromolar) increase the dose of Folinic Acid (see below)

If **72 hour** level is > 2 x 10^{-6}M (2 micromolar) increase Folinic Acid and give iv as calculated below

If **72 hour** level is < 2 x 10^{-6}M (2 micromolar) continue with Folinic 15mg/m^2 iv 6 hourly until level is < 1 x 10^{-7}M (0.1 micromolar)

During methotrexate infusion and folinic acid rescue:

Continue to ensure urine pH is > 7 by giving stat doses of Sodium Bicarbonate 3.0g orally or 50mls 8.4% iv.

Check daily U&Es, creatinine and alternate day FBC, LFTs

Monitor fluid balance carefully and give iv frusemide if fluid overload occurs or urine output falls to <400ml/m_2 in any 4-hour period.

Calculation of folinic acid rescue on the basis of plasma methotrexate levels

	Plasma methotrexate level (µmol/l)				
Time after starting MTX	<0.1	0.1 - 2.0	2.0 - 20	20 - 100	>100
48hrs	none[a]	15mg/m^2 q6h[b]	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h
72hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h
96hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h
120hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h
>120hrs	none	15mg/m^2 q6h	10mg/m^2 q3h	100mg/m^2 q3h	1g/m^2 q3h

a. No extra folinic acid required provided methotrexate levels are < 0.1µmol/l (10^{-7}M) at 48 hours
b. q6h = every 6 hours
c. At time points after 120 hrs folinic acid administration should be continued as recommended for time '120hrs after starting MTX'

Conversion table for methotrexate levels expressed in different units

molar (M)	µg/ml	ng/ml	µmol/l
1 x 10^{-3}	460.0		1013.0
2 x 10^{-4}	92.0		202.0
1 x 10^{-4}	46.0		101.0
2 x10^{-5}	9.2		20.0
1 x10^{-5}	4.6		10.1
2 x10^{-6}	0.92		2.0
1 x10^{-6}	0.46	460.0	1.01
2 x10^{-7}	0.092	92.0	0.2
1 x10^{-7}	0.046	46.0	0.10
2 x10^{-8}	0.010	9.2	0.02
1 x10^{-8}	0.005	4.6	0.01

Following Methotrexate infusion and Folinic acid rescue

Check FBC, U&Es, creatinine, LFTs at least twice during the week following the first and second cycles to detect any delayed toxicity that may occur.

Additional medications:

Pre-rituximab: Chlorphenamine 10mg iv, Hydrocortisione 100mg iv, Paracetamol 1g PO.
Ondansetron 8mg iv bd days 8 and 9
Dexamethasone 8mg iv od days 8 and 9
If already on an equivalent or higher dose of Dexamethasone, do not need to add in extra.
Metoclopramide 10mg tds prn. If <30 yr old or known reaction to metoclopramide use Cyclizine 50mg tds prn
Prednisolone 0.5% eye drops both eyes, 1 drop tds for 7 days starting on day 8,
Calcium folinate, mouthcare, Tumour Lysis prophylaxis (if required),

G-CSF: filgrastim 5mcg/kg subcutaneous daily starting day 11 with each cycle (all patients)

Consider adding Aciclovir, Fluconazole prophylaxis. Co-Trimoxazole 480mg days 11-18 only

Investigation prior to initiating treatment

ECOG PS 0-3 (0-2 if age >65)
Biopsy proven CNS lymphoma
HIV negative
Adequate bone marrow function:
- Plts ≥ 100
- Hb ≥ 90
- Neuts >2

U and Es
Renal- CrCL ≥ 60 ml/min by mC-G or clearance
Cardiac - LVEF ≥ 50% (or <50 yrs old with no cardiac history, risks or symptoms)
LFTs:
- Serum bilirubin ≤ 51 umol/L
- AST/ALT and γGT ≤ 2ULN

Cautions

Drug interactions:
The co-administration of **Co-trimoxazole/Trimethoprim** and methotrexate should be avoided as it can result in increased haematological toxicity.
NSAIDs and salicylates can reduce the clearance of methotrexate, resulting in increased toxicity.
Proton pump inhibitors can reduce clearance of methotrexate, resulting in increased toxicity. Change omeprazole/lansoprazole to Ranitidine 150mg bd if gastric protection required.
Avoid other nephrotoxic drugs e.g. Gentamicin

Penicillin based drugs can reduce clearance of methotrexate, resulting in increased toxicity. Avoid on days receiving methotrexate and until it is cleared (<0.1 micromolar). This includes avoiding TAZOCIN - if antibiotic monotherapy is needed for sepsis during methotrexate administration use Meropenem.

Comments: If low Hb prior to treatment, blood transfusion should be completed prior to high dose Methotrexate (transfusing after high dose Methotrexate will delay the clearance of Methotrexate).

Patient to avoid fizzy drinks with citric acid –can lower urinary pH levels, which reduces renal clearance of methotrexate.

Investigations and consultations prior to each cycle

FBC, U&Es, LFTs
Toxicity profile
Patient must be reviewed regularly by Dr Kennedy, Dr Kumar or current team registrar and seen on Day 0 prior to methotrexate administration. Patient fitness, toxicity and up to date blood tests to be reviewed. Drug chart to be reviewed to ensure no drugs with potential drug interactions are being used. Patient to be seen daily on ward by consultant/SPR.
Rituximab can be given on day 1 and 6 with telephone approval from consultant.

Acceptable levels for treatment to proceed (if outside these levels defer one week or contact consultant)

Hb>90
Neutrophil count >1.5
Platelet count >100

Monitor Renal function (including repeat 24hour creatinine clearance) with each cycle. Monitor Liver function tests.

Strict adherence to measuring urinary pH and ensuring levels are >7.
Urinary pH <7 (more acidic) reduces renal clearance of Methotrexate and greatly increases toxicity and delays clearance. Must be kept >7 with sodium bicarbonate 8.4% 50mls prn.

If toxicity with a particular drug is sufficient to mean it is not possible to give again, continue with other remaining drugs. Each drug has an independent benefit. E.g. if Methotrexate is discontinued, Rituximab, Thiotepa and Cytarabine can still be given.

Side Effects

Infusion related reactions, especially with Rituximab (see Rituximab protocol)
Bone marrow suppression :anaemia, thrombocytopenia, neutropenia, lymphopenia
Infection –neutropenic sepsis. Risk of pneumocystis pneumoniae. Risk of candidiasis. Risk of Varicella Zoster reactivation (shingles)
Cytarabine: ocular pain, foreign body sensation, photophobia and blurred vision. Dizziness, headache, confusion, cerebellar toxicity. Skin freckling, itching, rash, skin sloughing of the palmar and plantar surfaces. Myalgia and bone pain
Methotrexate: Renal failure (can be severe); consider dose reductions for patients with renal impairment, Gastrointestinal; nausea and vomiting, diarrhoea, stomatitis
Hepatotoxicity; risk is related to cumulative dose and prolonged exposure. Alcohol abuse, obesity, advanced age and diabetes may increase the risk
Pneumonitis, may occur at any time during therapy; monitor for pulmonary symptoms, particularly dry, non-productive cough
Photosensitivity and /or severe dermatologic reactions
Thiotepa: allergic reactions, dizziness, headache and blurred vision

Infertility and early menopause highly likely. Offer male patients sperm storage.

If severe renal impairment occurs or Methotrexate levels are persistently high recombinant **Glucarpidase/carboxypeptidase** can be administered to rapidly reduce plasma methotrexate levels. This drug can only be administered by involving prescribing consultant and senior pharmacist.

Dose Modification Criteria

Haematological Toxicity:

Neutrophils ≥ 1.0×10^9/L and platelets ≥ 100×10^9/L prior to each cycle.

Renal Impairment

Creatinine clearance (mL/min)	% dose
Cytarabine	
> 60	**100% dose**
46 - 59	**60% dose**
31 - 45	**50% dose**
< 30	**Discuss with Consultant**
Methotrexate (as per Renal drug Handbook) *	
> 50	**100% dose**
20 - 49	**50% dose**
< 20	**Discuss with Consultant**

***See renal drug handbook for alternative dosing regimes associated with other reference sources

Hepatic impairment

Bilirubin (µmol/L)		AST/ALT (IU/L)	Cytarabine	Methotrexate
≤ 34	**and**	**≤ 180**	**100% dose**	**100% dose**
34 - 50	**and**	**≤ 180**	**50% dose**	**100% dose**
51 - 85	**or**	**> 180**	**50% dose**	**75% dose**
>85			**50% dose**	**Contraindicated**

Thiotepa: limited information available regarding dose modification for renal and hepatic impairment Consider dose reduction, but no formal recommendations.

Specific Information on Administration

Strict adherence to measuring urinary pH and ensuring levels are greater than 7. Urinary pH <7 (more acidic) reduces renal clearance of methotrexate and greatly increases toxicity and delays clearance.

If any team professional involved in delivering this treatment has a concern or question they should always ask the prescribing consultant or senior chemotherapy pharmacist.

Additional advice for ward nurses and ward based doctors

1. Strict fluid balance is essential. Maintain and calculate fluid balance regularly
2. Check baseline weight on day 6 and check each day on the ward.
3. If >/= 2kg weight gain, >/=2Litre positive fluid balance, or signs of limb/sacral oedema give furosemide 40mg po
4. If signs of pulmonary oedema, give stat 40mg iv Furosemide
5. Ensure no nephrotoxic drugs are given and make sure no interacting drugs as listed above are commenced.
6. Start Folinic acid (calcium folinate) rescue at 24 hours, i.e. start of day 8
7. Take first plasma Methotrexate level at 48 hours from start of Methotrexate infusion, i.e. day 9, 9-10am. Send to laboratory urgently. Phone LTHTR lab to ensure is sent promptly to Alder Hey Hospital, Liverpool to be processed. Ensure the result is back by 5pm.

THIS PROTOCOL HAS BEEN DIRECTED BY DR S KENNEDY, CLINICIAN FOR CNS LYMPHOMAS

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

DATE **March 2016**
REVIEW **March 2018**
VERSION **4**