MATRIX (Methotrexate, Cytarabine, Thiotepa and Rituximab)

Indication
First line treatment of primary CNS lymphoma.

ICD-10 codes
Codes with a prefix C85.

Regimen details

Day	Drug	Dose	Route
1 and 6	Rituximab	375mg/m^2	IV infusion
7	Methotrexate	500mg/m^2	IV infusion
7	Methotrexate	3g/m^2	IV infusion
8 onwards	Calcium folinate	As below	IV/PO
8 and 9	Cytarabine	2g/m^2 **BD** (12 hours apart)	IV infusion
10	Thiotepa	30mg/m^2	IV infusion

Pre and post hydration required, to commence prior to methotrexate.

Note: may also be given in a condensed form, with rituximab given on days 1 and 6 (as above) and chemotherapy on days 2-5 as below:

Day	Drug	Dose	Route
1 and 6	Rituximab	375mg/m^2	IV infusion
2	Methotrexate	500mg/m^2	IV infusion
2	Methotrexate	3g/m^2	IV infusion
3 onwards	Calcium folinate	As below	IV/PO
3 and 4	Cytarabine	2g/m^2 **BD** (12 hours apart)	IV infusion
5	Thiotepa	30mg/m^2	IV infusion

Pre and post hydration required, to commence prior to methotrexate.

Cycle frequency
21 days

Number of cycles
Up to 4 cycles. Disease should be reassessed after 2 cycles before proceeding to 4 cycles.

Administration
Rituximab is administered in 500mL sodium chloride 0.9%. The first infusion should be initiated at 50mg/hour and if tolerated the rate can be increased by 50mg/hour every 30 minutes to a maximum of 400mg/hour. Subsequent infusions should be initiated at 100mg/hour and if tolerated increased by 100mg/hour increments every 30 minutes to a maximum of 400 mg/hour.

Methotrexate pre and post hydration:
1000mL sodium chloride 0.45%/dextrose 5% with 20mmoL potassium chloride and 50mmoL sodium bicarbonate should be commenced 8-24 hours prior to methotrexate at a suggested rate of 1000mL over 4 hours and continued concurrently during methotrexate infusion and until calcium folinate rescue is no longer required (see below).
Full dose methotrexate should only be given in the presence of a normal serum creatinine and CrCl ≥ 80mL/min. See below for dose reductions in renal impairment.

Prior to commencing methotrexate, patients must have a urine pH ≥7.0 and a urine output ≥ 100mL/hour. This should be maintained during treatment and until calcium folinate rescue is no longer required. Fluid balance should be closely monitored and urine pH measured hourly. Additional sodium bicarbonate (either added to fluids or given orally) may be required to maintain urine pH ≥7.0.

Methotrexate is given in 2 separate doses. Methotrexate 500mg/m^2 is administered in 250mL sodium chloride 0.9% over 15 minutes. This is then immediately followed by the 3g/m^2 dose administered in 1000mL sodium chloride 0.9% over 3 hours.

Calcium folinate is commenced 24 hours after the start of the first methotrexate infusion at a dose of 15mg/m^2 every 3 hours for 6-8 doses. It is administered as an IV bolus or IV infusion in 100mL glucose 5% over 30 minutes. Calcium folinate is then given every 6 hours until serum methotrexate level <0.1µmols/L. It may be given orally after the first 24 hours if the patient is compliant, not vomiting and otherwise without complication. Calcium folinate is available as 15mg and 30mg tablets.

Serum methotrexate levels should be taken 48 hours after the start of the methotrexate infusion and then every 24 hours. If the 48 hour level is >2.0µmols/L the dose of calcium folinate should be doubled. Serum methotrexate levels and U+Es must be checked every 24 hours and urine output and pH every hour. Calcium folinate rescue and urine pH should be maintained ≥7.0 until the methotrexate level is <0.1µmols/L. The dose of calcium folinate should also be increased if serum creatinine increases > 50% from baseline.

Cytarabine is administered in 1000mL sodium chloride 0.9% over 3 hours every 12 hours. At least the first dose will run concurrently with the post hydration fluid. A total of 4 doses are given.

Thiotepa is administered in 50-100mL sodium chloride (concentration dependent) over 30 minutes via a 0.2 µm in-line filter.

Pre-medication

Pre-hydration as above.
Rituximab premedication:

- Paracetamol 1g PO 60 minutes prior to rituximab infusion
- Chlorphenamine 10mg IV bolus 15 minutes prior to rituximab infusion
- Dexamethasone 8mg IV bolus or hydrocortisone 100mg IV bolus 15 minutes prior to rituximab infusion

Emetogenicity

This regimen has high emetic potential.

Additional supportive medication

Allopurinol 300mg OD (100mg OD if CrCl < 20mL/min) for the first 2 weeks.
Antiemetics as per local policy.
Mouthwashes as per local policy.
H_2 antagonist or PPI as per local policy.
GCSF as per local policy.
Antiviral, antifungal and PCP prophylaxis as per local policy.
Prednisolone 0.5% eye drops QDS for 7 days starting on day of first cytarabine dose (to avoid chemical conjunctivitis from high-dose cytarabine).
Calcium folinate as above.

Extravasation

Cytarabine, thiotepa and rituximab are neutral (Group 1)
Methotrexate is an inflammatant (Group 2)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC (with film)	72 hours and daily during treatment
U+E (including creatinine)	72 hours and daily during treatment
LFTs	72 hours and twice weekly during treatment

Consider echocardiogram and/or lung function tests if clinically indicated.
Hepatitis B and C serology
HIV status

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	Twice a week between cycles and 72 hours before next cycle
U+E (including creatinine)	Twice a week between cycles and 72 hours before next cycle
LFTs	Twice a week between cycles and 72 hours before next cycle
Serum methotrexate levels	As above

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	> 1.0 x 10^9/L
Platelets	> 100 x 10^9/L
Creatinine Clearance (CrCl)	≥ 80 mL/min
Bilirubin	≤ 1.5 x ULN
AST/ALT	≤ 3.5 x ULN

If pleural effusion or ascites present, methotrexate should not be given due to risk of accumulation and prolonged toxicity.

Dose modifications

- **Haematological toxicity**

Grade 3-4 cytopenias are expected with this regimen. Delay treatment if neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L until count recovery.

- **Renal impairment**

Discuss with consultant as some circumstances may warrant 100% dose.

CrCl (mL/min)	**Methotrexate dose**	**Cytarabine dose**
≥ 80	100%	100%
60-79	65%	
45-59	50%	60%
30-44	50%	50%
<30	Discontinue	Discontinue

If patient has raised creatinine **and** methotrexate level > 2.0 µmols/L, seek specialist renal advice.

There is limited information regarding thiotepa in renal impairment, consider dose reduction and use with caution.

- **Hepatic impairment**

Discuss with consultant as some circumstances may warrant 100% dose.

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Methotrexate dose**	**Cytarabine dose**
≤ 1.5	and	≤ 3.5	100%	100%
1.5 – 3	and	≤ 3.5	100%	50%
3 – 5	or	> 3.5	75%	50%
> 5			Discontinue	50%

The above parameters for transaminase levels for cytarabine refer to dose modifications at baseline and prior to subsequent cycles. Within a treatment cycle cytarabine dose should only be reduced to 50% if bilirubin > 1.5 x ULN irrespective of transaminase levels. Doses may be escalated in subsequent cycles in the absence of further toxicity (consultant decision).

Note: raised transaminases and/or bilirubin may occur for up to 2 weeks after methotrexate.

There is limited information regarding thiotepa in hepatic impairment, consider dose reduction and use with caution.

- **Other toxicities**

Toxicity	**Definition**	**Methotrexate**	**Cytarabine**
Cardiovascular	Grade 3-4	Interrupt treatment until resolved	Interrupt treatment until resolved
Coagulation	Grade 4	75% dose	75% dose
Gastrointestinal	Grade 4	75% dose	75% dose
Pulmonary	Grade 4	75% dose	75% dose

If pleural effusion or ascites present, methotrexate should not be given due to risk of accumulation and prolonged toxicity. Discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Cardiotoxicity
Neurotoxicity
Acute pulmonary toxicity
Nephrotoxicity
Hepatotoxicity
CNS toxicity (cytarabine)
Infertility

- **Frequently occurring side effects**

Myelosuppression
Diarrhoea
Infusion related reactions (rituximab)
Fatigue
Nausea and vomiting
Mucositis, stomatitis
Alopecia
Conjunctivitis (cytarabine)
Dizziness, headache, blurred vision (thiotepa)

- **Other side effects**

Haemorrhagic cystitis
Cytarabine syndrome (fever, myalgia, rash)
Hyperglycaemia
Myalgia, bone pain

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Methotrexate:
Avoid all nephrotoxic agents
NSAIDS: increase risk of methotrexate toxicity – avoid
Omeprazole: potential to increase methotrexate levels
Co-trimoxazole: if used concurrently may cause severe bone marrow depression – avoid
Theophylline: may reduce theophylline clearance – avoid
Acetretin: increased risk of hepatitis
Penicillins: may reduce excretion of methotrexate levels

Cytarabine:
Digoxin: cytarabine may affect plasma digoxin levels – consider monitoring

Thiotepa:
CYP2B6 inhibitors (including clopidogrel) and **CYP3A4 inhibitors** (including azole antifungals and macrolide antibiotics) may increase plasma concentration of thiotepa and reduce concentration of active metabolite; avoid concomitant use.

Cytochrome P450 inducers (including rifampicin and carbamazepine) may increase metabolism of thiotepa and therefore increase plasma concentration of the active metabolite.

Additional comments

It is expected that patients receiving high dose methotrexate will develop hypertransaminasaemia and occasionally hyperbilirubinaemia. These elevations can last up to 2 weeks following the methotrexate infusion.
Persistent hyperbilirubinaemia and/or grade 3-4 hypertransaminasaemia for longer than 3 weeks should result in discontinuation of treatment.

References

- Summary of Product Characteristics Methotrexate (Hospira) accessed 11 Nov 2015 via www.medicines.org.uk
- Summary of Product Characteristics Cytarabine (Pfizer) accessed 11 Nov 2015 via www.medicines.org.uk
- Summary of Product Characteristics Thiotepa (Adienne) accessed 18 May 2018 via www.medicines.org.uk
- Summary of Product Characteristics Rituximab (Roche) accessed 11 Nov 2015 via www.medicines.org.uk
- Ferreri AJ et al. Addition of thiotepa and rituximab to antimetabolites significantly improves outcomes in primary CNS lymphoma: first randomization of the IELSG32 trial. Presented at: 13th International Conference on Malignant Lymphoma; June 17-20, 2015; Lugano, Switzerland. Abstract 009

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