High Dose Methotrexate and Cytarabine

Indication

Treatment of primary CNS lymphoma.
May be an option for the treatment of CNS relapse of high grade lymphoma.

ICD-10 codes

Codes with a prefix C85

Regimen details

Day	Drug	Dose	Route
1	Methotrexate	500mg/m^2	IV infusion
1	Methotrexate	3g/m^2	IV infusion
2 onwards	Calcium folinate	As below	IV/PO
2	Cytarabine	2g/m^2 **BD** (12 hours apart)	IV infusion
3	Cytarabine	2g/m^2 **BD** (12 hours apart)	IV infusion

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

The above regimen is for patients < 75 years of age. For patients ≥ 75 years, discuss with consultant.

Cycle frequency

21 days

Number of cycles

2-4 cycles. Disease should be reassessed after 2 cycles before proceeding to 4 cycles.

Administration

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.
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 on days 2 and 3. A total of 4 doses are given.

Pre-medication

Pre-hydration as above.

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.
Prednisolone 0.5% eye drops QDS (to avoid chemical conjunctivitis from high-dose cytarabine)
Calcium folinate as above.

Extravasation

Cytarabine is 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.

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

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.

- **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%

Cytarabine dose should be reduced to 50% if bilirubin > 1.5 x ULN. Doses may be escalated in subsequent cycles in the absence of toxicity (consultant decision).

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

- **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.

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
Fatigue
Nausea and vomiting
Mucositis, stomatitis
Alopecia
Conjunctivitis (cytarabine)

- **Other side effects**

Haemorrhagic cystitis
Cytarabine syndrome (fever, myalgia, rash)

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

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 28 Jan 2015 via www.medicines.org.uk
- Summary of Product Characteristics Cytarabine (Pfizer) accessed 28 Jan 2015 via www.medicines.org.uk
- Ferreri AJM, Reni M, Foppoli M et al. High-dose cytarabine plus high-dose methotrexate versus high-dose methotrexate alone in patients with primary CNS lymphoma: a randomised phase 2 trial. Lancet 2009;374:1512-20

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