HIGH-DOSE METHOTREXATE PLUS HIGH-DOSE CYTARABINE

An option for treatment of CNS relapse of high grade lymphoma

Drugs/Dosages/Administration:

Day 0 (T= -12 hr)	**Hydration / Alkalinisation** – pre methotrexate (starting T = -12 hours; see below)	
Day 1 (T=0) Aim to start at 10am	**Methotrexate**	3500mg/m^2 IV infusion over 3 hours in exactly 1000ml sodium chloride 0.9%, concurrent with (compatible via Y-site connection): 500ml sodium chloride 0.9% + 35ml sodium bicarbonate 8.4% IV over 3 hours.
Day 2 (T=+24 hr)	**Folinic acid**	**Starting 24 hours after start of methotrexate:** 30mg IV bolus every 6 hours for at least 4 doses i.e. 24 hours, then change to oral route as tolerated at 30mg PO every 6 hours until methotrexate levels < 0.1 µmol/L. If methotrexate level > 2.0 µmol/L after 72 hours, the dose and frequency of folinic acid should be increased. See Comments on page 3 for further details.
Days 2 & 3	**Cytarabine**	2000mg/m^2 IV infusion **twice daily** in 500ml sodium chloride 0.9% over 1 hour There is a 12 hour interval between the start of each dose: administer at 24, 36, 48 and 60 hours after start of methotrexate.
Day 3 (T=+48 hr) .	**MTX levels**	Serum methotrexate levels should be obtained as follows:- 48 hours **after start** of the methotrexate infusion, then once daily until level is < 0.1 µmol/L, at which point folinic acid rescue is stopped RMH (Sutton) labs provide a methotrexate (MTX) monitoring service - ensure arrangements have been made for taxi/courier as appropriate and RMH pathology lab informed of dose and timing of methotrexate, plus our contact telephone number.
Day 8	**Filgrastim**	300 mcg (480 mcg if > 90kg) s/c od Day 8 to Day 14

Hydration/Alkalinisation:

Start at T = - 12 hours (ideally start at 10pm to ensure that methotrexate levels taken and measured within normal working hours):

Pre-MTX Hydration: 1 litre NaCl 0.9% + 70ml sodium bicarbonate 8.4% IV over 6 hours
then
1 litre NaCl 0.9% + 70ml sodium bicarbonate 8.4% IV over 6 hours

Check urine pH and only proceed with administration of methotrexate and concurrent IV sodium bicarbonate once pH > 7 (see Comments)

Post-MTX Hydration: a) Glucose 5% 1000ml + 50ml sodium bicarbonate 8.4% IV infusion, running at:
200ml/hour for BSA ≥ 1.6m^2;
150ml/hour for BSA < 1.6m^2
then:

b) Sodium chloride 0.9% 1000ml + 50ml sodium bicarbonate 8.4% + 20mmol KCl IV infusion, running at:
200ml/hour for BSA ≥ 1.6m^2;
150ml/hour for BSA < 1.6m^2

Alternate fluids a) and b) continuously until methotrexate level < 0.1µmol/l.

Monitor and maintain fluid balance and urine pH carefully throughout (see Comments)

Frequency: every 3 weeks for 4 cycles

Other Drugs: Allopurinol 300mg po daily, ideally starting 24 hours before chemotherapy – review after 2 weeks. Also see Alliance guidelines for management of tumour lysis syndrome.

Acetazolamide[1] 500mg po bd on Days 1, 2 and 3 (start before MTX infusion).

PCP prophylaxis – prescribe monthly pentamidine (to avoid complications with co-trimoxazole interaction with MTX) until patient has completed all chemotherapy, then once FBC has recovered (neutrophils > 1.0, platelets > 50) switch to co-trimoxazole according to unit practice/protocol.

Corticosteroid eye drops (e.g. Maxidex) from Day 2 to Day 8; one drop in each eye every 4 hours when awake, increasing to 2 hourly if eyes become sore.

Drug Interactions: Avoid NSAIDs, salicylates & sulpha drugs (eg co-trimoxazole) concurrently with high dose methotrexate because they may delay excretion of methotrexate.
If patient taking NSAIDs, they should be stopped if possible at least 72 hrs before the start of treatment, and not re-started until methotrexate level < 0.1 µmol/L.
Avoid concurrent nephrotoxic drugs, if possible.
Penicillins have been known to interact with methotrexate. Avoid penicillins until folinic acid rescue has stopped.
There are a few case reports of proton pump inhibitors delaying the clearance of methotrexate. Although information is limited, it is advisable to avoid concurrent use.

Main Toxicities: myelosuppression; mucositis; alopecia; conjunctivitis (cytarabine); CNS toxicity (cytarabine); nephrotoxicity (MTX); hepatotoxicity (MTX); tumour lysis syndrome (ensure pre-medicated with allopurinol and good hydration); ovarian failure; infertility

Anti-emetics: highly emetogenic on Days 1, 2 and 3

Extravasation: non-vesicants

Regular Investigations:

FBC	before each cycle, and alternate days whilst in-patient (if neutropenia or thrombocytopenia occur, monitor more frequently as indicated)
U&Es	daily whilst in-patient (contact doctor if serum creatinine rises)
LFTs	before each cycle, and twice weekly whilst in-patient
LDH	monthly
Cr^{51}-EDTA or 24hr urine	baseline (GFR needs to be > 60ml/min to proceed)
Methotrexate levels	starting at 48hr after MTX start
Urine output & pH	weight should be recorded twice daily and strict fluid balance chart should be maintained (see Comments)

Comments: Patients require a double lumen or triple lumen central venous catheter.

Maintaining adequate hydration and urine output are essential for rapid clearance of high dose methotrexate. Methotrexate can precipitate in the kidney tubules and directly induce tubular injury. The risk is increased in the presence of acidic urine, with volume depletion, and when high plasma MTX concentrations are sustained.

A fluid space (e.g. ascites, pleural effusion) is a contra-indication for high-dose methotrexate as the methotrexate can accumulate and cause prolonged toxicity.
During methotrexate administration and until methotrexate levels < 0.1µmol/L, monitor fluid balance and urine pH carefully:

Methotrexate infusion should not start until urine pH is > 7. Check urine pH every time urine is passed.
Urine pH should be ≥ 7.0 at the start, during methotrexate infusion and throughout folinic acid rescue.

- If urine pH remains < 7 after pre-hydration fluid, 50 – 100mmol sodium bicarbonate over 30 minutes will need to be given (and urine re-checked) before starting methotrexate.
- If urine pH < 7 at a later stage, add either 1.5g sodium bicarbonate capsules orally qds + prn, or further IV bicarbonate. Acidic fruit juices should be avoided.

Weight should be recorded twice daily and a strict fluid balance chart should be maintained. If there is a weight increase of 2kg, a positive fluid balance of 2 litres, or symptoms of fluid overload, furosemide 20 - 40mg po should be given.
A urine output of less than 400ml / m^2 / 4 hours (approx. 700ml over 4 hours) is also an indicator for furosemide administration.

Folinic acid rescue: The schedule given above is normally sufficient unless problems are encountered with renal function or alkalinisation. If methotrexate level fails to fall at the desired rate, prescribe and administer folinic acid as follows:

Time after starting MTX	Methotrexate Plasma Concentration (µmol/L)			
	0.1 - 2	2 - 20	20 - 100	> 100
48h	30mg q 6h	15mg/m^2 q 6h	10mg/m^2 q 3h	100mg/m^2 q 3h
72h	30mg q 6h	10mg/m^2 q 3h	100mg/m^2 q 3h	1000mg/m^2 q 3h
96h	30mg q 6h	10mg/m^2 q 3h	100mg/m^2 q 3h	1000mg/m^2 q 3h
120h	30mg q 6h	10mg/m^2 q 3h	100mg/m^2 q 3h	1000mg/m^2 q 3h

Notes: Folinic acid 1000mg/m^2 dose to be infused centrally (neat, via syringe driver) over 15 - 30 minutes. Contact pharmacy for minimum volume of fluid if giving peripherally.

Glucarpidase: NHSE will fund glucarpidase (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (dose >1g/m^2):

- who develop significant deterioration in renal function (>1.5x ULN and rising), or the presence of oliguria) ***OR***
- who have toxic plasma methotrexate level **and** have been treated with all standard rescue and supportive measures **and** are at risk of life-threatening methotrexate-induced toxicities.
  The recommended dose is one single intravenous injection of 50units/kg.

No stocks are held within the Alliance, but it is supplied on a named-patient basis from Clinigen.

Dose Modifications

Haematological Toxicity: Proceed each cycle only once neutrophils > 1.0 x 10^9/l and platelets > 100 x 10^9/l
If low counts are thought to be due to marrow infiltration, discuss with Consultant.

Renal Impairment: Patient must have a measured GFR of > 60ml/min to proceed with this regimen.
Repeat Cr^{51}-EDTA / 24 hour urine if the result is borderline at the start of treatment or if there is a 30% change in serum creatinine.

Hepatic Impairment: Methotrexate is contraindicated in severe hepatic impairment.
Note that raised transaminases / bilirubin may occur for up to two weeks following each methotrexate dose, but this does not require discontinuation of further methotrexate unless transaminases are > 5 x ULN or persistent hyperbilirubinaemia for more than 3 weeks.

Bilirubin (µmol/L)	Cytarabine Dose
21 – 34	Give 100% dose
> 34	Give 50% dose

Patient Information: Macmillan leaflets for Methotrexate and Cytarabine

References: Ferreri, AJM et al; Lancet 2009; 374: 1512 - 1520
Stockley's Drug Interactions via Medicines Complete, accessed 17/01/13
[1]Shamash, J et al; Cancer Chemother Pharmacol 1991: 28 (2): 150 - 151