

## HIGH DOSE METHOTREXATE for CNS prophylaxis

An option for prophylaxis of CNS disease in high risk non-Hodgkin's lymphoma, alongside a curative regimen (usually R-CHOP)

Drugs/Dosages/Administration:

**Pre-hydration to start on day 14 / HD MTX to start on day 15 of: Cycle 2 and Cycle 4 R-CHOP**

<b>T = -12 hr</b>	<b>Hydration / Alkalinisation</b> – pre methotrexate (starting 12 hours before start of MTX infusion; see below for details)
<b>T = 0</b> <i>Aim to start at 10am of day 15 R-CHOP</i>	<b>Methotrexate</b> 3000mg/m <sup>2</sup> 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 hrs
<b>T = +24 hr</b>	<b>Folinic acid</b> <b>Starting 24 hours after start of methotrexate:</b> 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.
<b>T = +48 hr</b>	<b>MTX levels</b> Serum methotrexate levels should be obtained as follows:- 48 hours <b>after start</b> 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.

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

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: 2 doses, given on Day 15 of Cycle 2 R-CHOP, and Day 15 of Cycle 4 R-CHOP

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**Other Drugs:** Acetazolamide<sup>1</sup> 500mg po bd on Days 1, 2 and 3 (start before MTX infusion).  
 G-CSF support will be required for all patients post R-CHOP, in order to avoid a delay in starting MTX.  
 A further short course of G-CSF, to start 24 hours post MTX infusion end (when folinic acid starts), may also be considered.

**Drug Interactions:** Co-trimoxazole or trimethoprim should be avoided with methotrexate, as this can result in increased haematological toxicity.  
 A number of drugs can interfere with tubular secretion of methotrexate. These include penicillins, aspirin and NSAIDs.  
 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 penicillins, including tazocin, until folinic acid rescue has stopped.  
 Avoid concurrent nephrotoxic drugs, if possible.  
 There are a few case reports of proton pump inhibitors delaying the clearance of MTX. Although information is limited, it is advisable to avoid concurrent use.

**Main Toxicities:** myelosuppression; mucositis; nephrotoxicity; hepatotoxicity; ovarian failure; infertility

**Anti-emetics:** highly emetogenic

**Extravasation:** non-vesicant

**Regular Investigations:** Cr<sup>51</sup>-EDTA or 24hr urine baseline (GFR needs to be > 60ml/min to proceed)  
 Pregnancy test before each dose, for women of child-bearing potential  
 FBC before each dose  
 U&Es before each dose and daily whilst in-patient (contact doctor if serum creatinine rises)  
 LFTs before each dose  
 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 at high risk of CNS relapse include those with high grade lymphoma and *either*: raised LDH plus more than one extra-nodal localisation (spleen not regarded as extra-nodal, and two lesions in the same system are regarded as a single extra-nodal localisation)  
*or*:  
 anatomical sites – testicular\*, breast or involving epidural space  
 \* *however, follow BCSH guidance for patients with primary testicular lymphoma i.e. intrathecal MTX x 4 doses (provided there are no other areas of involvement, which would warrant HD MTX in combination with intrathecal therapy)*

Patients require a double 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 < 0.1 µmol/L, monitor fluid balance and urine pH carefully:

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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<sup>2</sup> / 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 alkalisation. If methotrexate level fails to fall at the desired rate, the dose and frequency of folinic acid should be increased as in the table below:  
(and start to consider the potential need for glucarpidase - see Renal Impairment section)

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

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

## Dose Modifications

**Haematological Toxicity:** Proceed with each cycle only once neutrophils > 1.0 x 10<sup>9</sup>/L and platelets > 75 x 10<sup>9</sup>/L

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

In the event of a significant deterioration in renal function (> 1.5 x ULN and rising), associated with toxic plasma methotrexate levels and if, despite folinic acid rescue, the patient is at risk of life-threatening methotrexate induced toxicities, **glucarpidase** (50 units/kg as a single IV injection) is routinely funded. No stocks are held within the Alliance, but it is supplied on a named-patient basis from Clinigen.

**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.

**Patient Information:** Macmillan leaflet for Methotrexate

**References:** Abramson, J et al; Cancer 2010; 116 (18): 4283 - 4290  
 1Shamash, J et al; Cancer Chemother Pharmacol 1991; 28 (2): 150 - 151  
 McMillan, A et al; Br J Haem 2013; 163: 168 - 181

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