Appendix 15: Guideline for the administration of Intravenous High-Dose Methotrexate

Regimen for administration of high-dose methotrexate

NOTE: The guidance for administration of high dose methotrexate is a detailed suggestion for trial participants to follow. It contains all the necessary information to give the drug safely. However, those centres who have a firm local policy in place which differs in administration detail (but not dose) from the suggestions put forward here can administer high dose methotrexate within UKALL14 according to their local policies.

One week before admission for the 1st methotrexate infusion the Creatine Clearance (measured according to local practice) should be determined. The initial Creatinine Clearance before starting methotrexate should ideally be > 100 mls/minute.

Patients with a clearance between 80-100 mls / minute before the first dose of High Dose Methotrexate MUST have a measured Creatinine clearance (24 urine collection) BEFORE the second dose and dose adjustments (as above) made if the result is less than 80 mls /minute.

Also repeat Creatinine Clearance before the 2nd infusion if there is delayed methotrexate excretion after the first course.

Based on a dose of 3g/m^2 of Methotrexate and renal function pre-treatment use Dose reductions as follows:

Pre Cycle 1

CrCl(ml/min)	Dose
> 80 mls/min	100%
50-80 mls/min	50 %
<50 mls/min	0 %

Pre Cycle 2

CrCl(ml/min)	Dose
> 50 mls/min	100%
<50 mls/min	0 %

Consult the TMG if in any doubt regarding the high dose methotrexate.

METICULOUS ATTENTION SHOULD BE PAID AT ALL TIMES TO CHANGES IN CREATININE CLEARANCE DURING THE HIGH DOSE METHOTREXATE PHASE. (BOTH WITHIN AND BETWEEN EACH COURSE OF METHOTREXATE).

On admission for each methotrexate infusion, measure:

- Serum creatinine
- Bilirubin and AST or ALT
- Plasma sodium and potassium
- FBC

Guidelines for dosing high dose methotrexate in Liver impairment

Bilirubin (micromol/L)	AST	Dose
<50	And < 180	100%
51-85	Or > 180	75%
> 85		Contraindicated

It is expected that patients receiving high dose methotrexate will develop hypertransaminasemia and occasionally hyperbilirubinemia.These elevations can last up to 2 weeks following the methotrexate infusion and are not considered toxicities requiring discontinuation of repeated administration of methotrexate. Persistant hyperbilirubinemia and/or grade 3-4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of the drug. Dose reduce, particularly in patients with concomitantly impaired renal function. The drug is contraindicated in severe hepatic impairment.

Pre-hydration - For at least 6 hours prior to the commencement of the intravenous methotrexate.

Hydration fluid - 1 litre dextrose saline to which has been added 50 mmol sodium bicarbonate and 20 mmol potassium chloride.

Infusion rate - 125 ml/m^2/hour.

Check urine pH - Adjust the sodium bicarbonate concentration to maintain the urinary pH between 7 and 8 (i.e. alkaline). A urinary pH of 7.5 or greater must be achieved before starting the methotrexate infusion.
Alternating bags of sodium chloride 0.9% and glucose 5% is acceptable.

HIGH-DOSE METHOTREXATE INFUSION
Methotrexate dose
Methotrexate 3 g/m^2 with:
10% (i.e. 300 mg/m^2) given over 1 hour (loading dose) in 200 mls sodium chloride 0.9%
90% (i.e. 2700 mg/m^2) given over next 23 hours in 1 litre sodium chloride 0.9%

NOTE: The infusion of methotrexate must always stop at 24 hours even if not completed for any reason.

FOLINIC ACID RESCUE MUST START AT 36 HOURS FROM THE START OF METHOTREXATE.
The first dose of folinic acid (to be given at 36 hours after the start of methotrexate infusion) must be written up at the time of prescribing the methotrexate infusion.

Dosage of folinic acid:
At 36 hours: Give 15 mg/m^2 iv.
36-48 hours: Give 15 mg/m^2 iv every 3 hours.
From then on: Give doses as per table below until methotrexate level is less than 0.1micromol/litre.

Monitoring of plasma methotrexate levels following infusion.
Times given are from time 0 (time of starting intravenous methotrexate infusion).
The following plasma samples are **required for patient's safe rescue** with folinic acid:
48 hours, 72 hours, and then every 24 hours until methotrexate level is less than 0.1micromol/litre

Table for the calculation of folinic acid rescue on the basis of MTX plasma levels.

Time after starting MTX	**MTX plasma concentration (micromol/litre)**				
	<0.1	0.1-2	2-20	20-100	>100
48h	None[a]	15mg/m^2q6h[b]	15mg/m^2q6h	10mg/m^2q3h	100mg/m^2q3h

72h	None	15mg/m^2q6h	10mg/m^2q3h	100mg/m^2q3h	1g/m^2q3h
96h	None	15mg/m^2q6h	10mg/m^2q3h	100mg/m^2q3h	1g/m^2q3h
120h[c]	None	15mg/m^2q6h	10mg/m^2q3h	100mg/m^2q3h	1g/m^2q3h

Notes

a No extra folinic acid is required provided MTX levels are below 0.1 micromol/litre at 48h.
b Dose and schedule of folinic acid: q6h = every 6 hours.
c At time points after 120h folinic acid administration should be continued as recommended for 120h.

Hydration regimen during and after completion of intravenous methotrexate infusion

Continue to infuse at a rate of 125 ml/m^2/hour for a minimum of 48 hours after start of methotrexate with:
1L dextrose saline containing 50 mmol of sodium bicarbonate and 20 mmol potassium chloride.
Alternating bags of sodium chloride 0.9% and glucose 5% is acceptable.
Continue to ensure that urinary pH is above 7 by adjusting sodium bicarbonate dose.

After 48 hours from the start of the intravenous methotrexate, **ENSURE** a combined oral and/or intravenous intake greater than 3 litres/m^2/24 hours until plasma methotrexate levels<0.1 micromols/litre.

Check fluid balance at regular intervals (at least 4-hourly) through each day, taking early action if fluid overload occurs by giving furosemide if the urine output falls below 400 ml/m^2 in any given 4-hour period.

Other investigations during folinic acid rescue:
Daily Creatinine, sodium and potassium.
Alternate days Bilirubin, AST, ALT, albumin, full blood count.

These investigations should also be checked at least twice during the week following the first and second methotrexate infusion to detect any toxicity that might occur.

Conversion table for methotrexate levels expressed in different units

Molar (M)	**µmol/l**
1×10^{-3}	1013.0
2×10^{-4}	202.0
1×10^{-4}	101.0
2×10^{-5}	20.0
1×10^{-5}	10.1
2×10^{-6}	2.0
1×10^{-6}	1.01
2×10^{-7}	0.2
1×10^{-7}	0.10

Drug interactions

Drugs which compromise renal function eg. aminoglycosides and cisplatin can decrease clearance of methotrexate and lead to systemic toxicity. Avoid concurrent use of Non steroidal anti inflamatories **(NSAIDs) including salicylates and sulphonamides**.
Large doses of penicillin may interfere with the active renal tubular secretion of methotrexate.
It is recommended that prophylactic co-trimoxazole be stopped one week before high dose MTX therapy, until maintenance therapy starts.