UKCCSG

CHEMOTHERAPY STANDARDISATION GROUP

METHOTREXATE

Version 1

METHOTREXATE

SECTION ONE

• Alternative Names

Amethopterin, α-Methopterin, MTX.

• Mechanism of action

Methotrexate (MTX) is an analogue of folic acid which penetrates into cells via a specific membrane transport system used by physiological folates.[1] Inside the cell MTX rapidly binds to and inhibits its target enzyme dihydrofolate reductase (DHFR), leading to the inhibition of the syntheses of purines and pyrimidines. Intracellular folates exist physiologically in the form of polyglutamates and MTX is also metabolised to polyglutamate forms. Recent data suggest that the syntheses of purines and thymidylate can be stopped by direct inhibition from dihydrofolate and MTX polyglutamates. Thus, following the inhibition of DHFR by MTX, increasing levels of the dihydrofolate polyglutamates may directly block the syntheses of these nucleotides, thus in addition to direct inhibition of DHFR by methotrexate, the formation of polyglutamyl metabolites of the drug is also thought to:

a) increase intracellular drug accumulation

b) increase intracellular drug retention

c) inhibit folate-dependent nucleotide synthesis, by effects at loci other than DHFR

High-dose methotrexate (HDMTX) regimens designed to circumvent MTX resistance are thought to act by overcoming the decreased membrane transport of MTX into tumour cells. Achieving and sustaining high plasma levels of the drug promotes MTX diffusion thus overcoming the defective MTX transport system. However, other possible mechanisms i.e. mutation or overproduction of DHFR and impaired polyglutamation have been identified.
The doses of methotrexate needed to achieve these high plasma concentrations MUST be followed by the antidote FOLINIC ACID (leucovorin) to prevent increased toxicity to normal tissues.

FOLINIC ACID (leucovorin) RESCUE [4,5,10]

The clinical usefulness of folinic acid rescue regimens is based upon the **selectivity** of the antidote in rescuing normal but not neoplastic tissue *plus* the **competitive** nature of the rescue in that more folinic acid is required to rescue at higher MTX concentrations.
Folinic acid can interact with MTX at different levels within the cells.

Membrane interactions

Folinic acid can compete with MTX uptake into cells since both use the same transport system. This observation forms the basis for one of the hypotheses of selectivity since tumour cells with a defect in the folate transport system would not be rescued since insufficient folate

would enter the cell; in contrast to normal cells with intact folate transport which could be more easily rescued.

Replenishment of reduced folates

Folinic acid provides the cell with a source of reduced folate cofactors which can be used to restore purine and pyrimidine synthesis even though the activity of DHFR remains impaired by the presence of dihydrofolate and MTX polyglutamates. This could account for the competitive nature of leucovorin rescue.

Inhibition of polyglutamate formation

Folinic acid can inhibit the formation of MTX polyglutamates. Some tumour cells containing MTXPG's can only be poorly rescued by folinic acid since nucleotide synthesis remains inhibited by the polyglutamates despite high intracellular levels of reduced folates. Since normal bone marrow precursors metabolise less MTX to polyglutamates they are less sensitive to the effects of MTX and can be more easily rescued with folinic acid.

- **Considerations prior to Intermediate/high-dose chemotherapy**

To prevent renal damage, intravenous hydration and alkalinisation is given **before** methotrexate is commenced and **continued** until plasma methotrexate levels are

< 0.2 μmol/l (2 x 10^{-7} M)

The establishment of an alkaline diuresis during treatment is important to increase the solubility of MTX and its 7-hydroxy metabolite and prevent the nephrotoxity resulting from precipitation of these substances in the renal tubules.

The appropriate folinic acid regimen **MUST** be prescribed at the same time as the MTX. **IV folinic acid** is commenced **24 or 36 hours** after the **start** of the MTX and treatment is continued until plasma MTX levels are **< 0.2 μmol / l (2 x 10^{-7} M)**
Details of the appropriate folinic acid dosing schedules in current protocols are shown in following table:

	FOLINIC ACID	REGIMEN
UKALL XI 92 NHL (904) UKALL INFANT 1 UKALL R1	START 36 HOURS AFTER COMMENCING METHOTREXATE INFUSION	15mg/m^2 EVERY 3 HOURS x 5 DOSES then 15mg/m^2 EVERY SIX HOURS TILL MTX < 1 x 10^{-7} M
NHL 901	START 24 HOURS AFTER COMMENCING METHOTREXATE INFUSION	15mg/m^2 IV EVERY SIX HOURS TILL MTX < 1 x 10^{-7}M (Minimum 8 Doses/ five IV)

NHL 902 COPADM 1,2,3	**START 24 HOURS AFTER COMMENCING METHOTREXATE INFUSION**	**15mg/m^2 IV EVERY SIX HOURS TILL MTX < 1 x 10 $^{-7}$M**
NHL 903 COPADM 1,2,3	**START 24 HOURS AFTER COMMENCING METHOTREXATE INFUSION**	**15mg/m^2 IV EVERY SIX HOURS TILL MTX < 1 x 10 $^{-7}$M**
BABY-BRAIN (CNS 9204)	**START 36 HOURS AFTER COMMENCING METHOTREXATE INFUSION**	**15mg/m^2 x 3 HOURLY X 5 DOSES then 15mg/m^2 x 6 HOURLY TILL MTX < 1 X 10 $^{-7}$M (Minimum 8 Doses)**
NHL FAB/LMB96	**START 24 HOURS AFTER COMMENCING METHOTREXATE INFUSION**	**15 mg/m^2 (po) EVERY SIX HOURS x 12 DOSES TILL MTX < 0.15 µmol/l**

Consider methotrexate dose reduction or avoid use in renal impairment when GFR < 60 ml/ min/ 1.73 m^2

In renal impairment higher serum methotrexate levels will occur, which will need higher doses of folinic acid rescue. Modifications of folinic acid dosing are detailed in the following section

- **Adverse effects**

With low oral dose: mouth ulcers, skin rashes, myelosuppression

With intermediate / high IV dose:

Common. Skin rashes, mild nausea/vomiting, myelosuppression (usually mild)

Occasional Mucositis * , enteritis.

Rare. Acute renal failure, hepatotoxicity, neurotoxicity.

* If mucositis severe then consider folinic acid mouthwash. Rinse with 10 ml of a solution of folinic acid 1 mg / ml four times daily.

SECTION 2

- **Recommended methods of administration**

In order to ensure the patients safe rescue with folinic acid after methotrexate administration, the following **plasma sample times are mandatory**:

Times after **start** of MTX administration

48 hours

72 hours and then every 24 hours if not completely rescued ***i.e.*** if plasma MTX **not** < 0.2 μmol / l ($2x10^{-7}$ M)

- **Methotrexate dosage**. As per protocol.

- **Methotrexate infusion details.**

Methotrexate will be given by IV infusion over **3 hours** or **24 hours** depending on protocol. When administered as a **24 hour infusion**, **10%** of the total dose should be administered in the **first hour** and the balance **(90%)** over the **next 23 hours**.

Folinic acid rescue will start **24 hours** after the **start** of the **3 hour** infusion, and **36 hours** after the **start** of **24 hour** infusion

Hydration Protocol

Hydration fluid:
Glucose 4%, Sodium chloride 0.18%
Potassium chloride **20 mmol / litre**
Sodium bicarbonate **50 mmol / litre**

Infusion rate 125 ml / m^2 per hour (3 litres / m^2 / 24 hours)

Urine pH A urinary pH >7 must be achieved before starting the MTX infusion. It may be necessary to increase the sodium bicarbonate concentration in the hydration fluid to **70 mmol / l** to maintain an alkaline urine (pH 7-8).

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

Hydration during MTX infusion

The MTX must be infused at the appropriate rate, in combination with the hydration fluid at a combined rate of 125 ml / m^2 / hour.

continued:

Hydration after completion of methotrexate infusion

Continue with hydration infusion at 125 ml / m^2 / hour for a minimum of 48 hours, ensuring that urinary pH is always >7 . After 48 hours **ENSURE** a combined oral and/or intravenous intake greater than 3l / m^2 / 24 hours until plasma methotrexate levels are < 0.2 μmol / l .

Folinic Acid Rescue

The folinic acid **MUST** be written up at the same time as the methotrexate is prescribed. Rescue starts **24 hours** after **start** of
3 hour MTX infusions and
36 hours after **start of 24 hour MTX infusions**

Dosage of folinic acid

3 hour MTX infusion:

Note: Time after **start** of methotrexate infusion

At **24 hours** give **15 mg / m^2 IV** every **3 hours** for **5 doses**

then **15 mg / m^2 IV** every **six hours** till rescued **(MTX level < 0.2 μmol / l)**

24 hour MTX infusion

Note: Time after **start** of methotrexate infusion

At **36 hours** give **15 mg / m^2 IV** every **3 hours** for **5 doses**

then **15 mg / m^2 IV** every **six hours** till rescued **(MTX level < 0.2 μmol / l)**

if 48 hour MTX level is greater than 20 μmol / l (>2x10^{-5}M)
then increase the dose of folinic acid IV*

if 72 hour MTX level is greater than 2 μmol / l (>2x10^{-6}M)
then increase the dose of folinic acid IV*

if 72 hour MTX level is less than or equal to 2 μmol / l (2x10^{-6}M) then continue folinic acid 15mg / m^2 IV every 6 hours until level is < 0.2 μmol / l .
Folinic acid may be given orally if the child is not vomiting

* for details of how to calculate the appropriate dose increases of folinic acid consult the table on the following page:

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

All doses by intravenous injection

Time after starting MTX	MTX plasma concentration (μmol/l)				
	<0.2	0.2 - 2	2 - 20	20 - 100	> 100
48 h	None [a]	15 mg/m² q6h[b]	15 mg/m² q6h	10 mg/m² q3h	100 mg/m² q3h
72 h	None	15 mg/m² q6h	10 mg/m² q3h	100 mg/m² q3h	1g/m² q3h
96 h	None	15 mg/m² q6h	10 mg/m² q3h	100 mg/m² q3h	1g/m² q3h
120 h [c]	None	15 mg/m² q6h	10 mg/m² q3h	100 mg/m² q3h	1g/m² q3h

Notes

a . No extra folinic acid is required provided MTX levels are below 0.2 μmol/l ($2x10^{-7}$ M) at 48 hours
b . Dose and schedule of folinic acid; q6h = every six hours
c . At time points after 120 hours, folinic acid administration should be continued as recommended for 120 hours

NOTE: In the face of severe clinical toxicity the dose of folinic acid can be increased

• Intrathecal Methotrexate

INTRATHECAL METHOTREXATE
< 1 year - 5mg
1- 2 years - 7.5mg
2 -3 years - 10mg
> 3 years - 12.5mg

• Drug interactions

Drugs which compromise renal function e.g. aminoglycosides and cisplatin can decrease clearance of methotrexate and lead to systemic toxicity. Avoid concurrent use of NSAID's, including salicylates and sulphonamides. Large doses of penicillin may interfere with the active renal tubular secretion of methotrexate.[6] In those protocols incorporating high-dose methotrexate (e.g. UKALL-XI), prophylactic co-trimoxazole must be stopped one week before HDMTX therapy.[9]

SECTION 3

• Dilution specification and stability

All methotrexate solutions are preservative-free
Presented as sterile, isotonic solutions with pH adjusted to 8.5; or as freeze dried powder for reconstitution with Water for Injections BP.
Manufacturers are limited by the terms of the product licence in respect of the stability and compatibility of MTX solutions in clinical practice.
However, a large body of information exists relating to the stability profile of methotrexate.[7,8]

- **Safe handling**

Methotrexate is non-vesicant and is not likely to be absorbed through intact skin.
However, the solution is irritant and skin contact should be avoided. In case of skin contact wash with water and consider emmolient cream to soothe inflamed areas. Irrigate eyes with copious amounts of water or saline. If significant amounts are inhaled or injected then consider cover with folinic acid.[7]

- **Clinical pharmacokinetics of methotrexate** [2,3]

Oral dosing

Large inter individual variations are expressed in the **rate** and **extent** of the absorption of methotrexate.

Mean oral bioavailability **33%** (13% - 76%)

With doses > 40mg/m^2 **17.5%** (12.7% - 22.3%)

The presence of food **decreases** oral bioavailability

Intravenous dosing

After IV bolus, plasma half-lives ($T_{1/2}$) :

phase		**Value $T_{1/2}$**
α	- tissue distribution -	2 - 8 minutes
β	- excretion and metabolism -	0.9 - 2 hours
γ	- MTX release from cells -	5.5 - 11 hours

- Between 40 -50% of MTX is bound to plasma protein, primarily albumin. At MTX concentrations > 5 x 10^{-5} M binding is saturated, resulting in increased concentrations of the free drug.

Dose-dependent MTX pharmacokinetics have been demonstrated over a dose range of 0.5 - 33.6 g/m^2/24 hours. There is a significant

correlation between dose and steady-state concentration (C_{ss}) but increase in dose is accompanied by a disproportionate increase in C_{ss}. Higher doses result in a shorter $T_{1/2}$, lower volume of distribution at steady-state and slower systemic clearance.

- **Third space distribution** into pleural or ascitic fluid after MTX may provide a source of prolonged release which can extend the terminal phase of drug excretion.

Age dependence

Children aged 1 - 4 years show significantly lower plasma steady-state levels, faster systemic clearance and higher volume of distribution.

- **Pharmacodynamics**

In general, the **severity of toxicity** is more dependent on the **duration of drug exposure** than on the absolute MTX concentration.

Although High Dose MTX is generally well tolerated, unpredictable life-threatening toxicity can occur. For patients who have markedly delayed clearance of MTX secondary to renal dysfunction, therapeutic options are few and of limited efficacy. **Carboxypeptidase-G2** inactivates MTX by hydrolysing its C-terminal glutamate residue. CPDG-2 may be used to rescue patients with renal dysfunction and delayed MTX excretion [12,13]

CPDG-2 must be administered as part of an NCI protocol [11],

UK contacts to obtain CPDG-2:

Duramed *Europe*	**Dr R Sherwood. ☎ 01865 784730**
CAMR	**Dr P Hambleton (Fax) 01980 610848** **Dr C Davies (Fax) 01980 611384**
NCI	**DR P Adamson. ☎001 301 496 1756 or 7386**

SECTION 4

- **Methotrexate protocols**

Low oral dose In ALL continuing therapy.
Dose 20 mg/m^2 at weekly intervals.

Low intrathecal dose In ALL, NHL and parameningeal RMS.
Intracranial germ-cell tumours
Dose 7.5 - 15mg depending on age and protocol.
Intrathecal doses to be administered 24 -26 hours after start of HDMTX

Intermediate IV dose In NHL and intracranial germ-cell tumours.
Dose 0.5 - 1 g/m^2 at varying intervals.

High IV dose In ALL, NHL and some CNS tumours.
Dose 3 - 8 g / m^2 at varying intervals.

For details of methotrexate dose and scheduling in current protocols see the following tables:

	MTX DOSE	MTX SCHEDULE	PRE-HYD	HYD. RATE	POST-HYD	HYDRATION SOLUTION
UKALL XI 92 NHL (904) UKALL R1 UKALL INFANT 1	6g/m^2 8g/m^2 8g/m^2	10% - 1 HOUR 90% - 23 HOURS	6 HOURS MINIMUM	31/m^2 /day	48 HOURS MINIMUM TILL MTX <1 x 10^{-7} M	GLUCOSE 5% SODIUM CHLORIDE 0.45% POTASSIUM CHLORIDE 20mmol/l SODIUM BICARBONATE 50mmol/1
NHL 903 COPADM 1,2,3	8g/m^2	3 HOURS	6 HOURS MINIMUM	31/m^2 /day	48 HOURS MINIMUM <1 x 10^{-7} M	GLUCOSE 4% SODIUM CHLORIDE 0.18% SODIUM BICARBONATE 50mmol/1
BABY-BRAIN (CNS 9204)	8g/m^2	10% - 1 HOUR 90% - 23 HOURS	3 HOURS MINIMUM	31/m^2 /day	48 HOURS MINIMUM <1 x 10^{-7} M	GLUCOSE 2.5% SODIUM CHLORIDE 0.45% SODIUM BICARBONATE 50mmol/1
NHL 902 COPADM 1,2,3	3g/m^2	3 HOURS	6 HOURS MINIMUM	31/m^2 /day	48 HOURS MINIMUM TILL MTX <1 x 10^{-7} M	GLUCOSE 4% SODIUM CHLORIDE 0.18% SODIUM BICARBONATE 50mmol/1
NHL 901	1g/m^2	33% - 1 HOUR 66% - 6 HOURS	4 HOURS	31/m^2 /day	MINIMUM 24 HOURS	GLUCOSE 4% SODIUM CHLORIDE 0.18% SODIUM BICARBONATE 50mmol/1
NHL FAB/LMB 96	3g/m^2 8g/m2	3 HOURS GROUP(B) 4 HOURS GROUP©	2 HOURS MINIMUM (urine pH >7)	3l/m^2 /day	(B) 48HRS (C) ©72HRS till MTX < 0.15µmol/l	GLUCOSE 5% SODIUM BICARBONATE 50 mmol/l POTASSIUM CHLORIDE 20 mmol/l

	INTRATHECAL METHOTREXATE

UKALL XI 92 **NHL (904)** **UKALL INFANT 1**	**< 1 year - 5mg** **1- 2 years - 7.5mg** **2 -3 years - 10mg** **> 3 years - 12.5mg** **< 1 year - 5mg** **1- 2 years - 7.5mg**
NHL 901 **(Head & Neck Primary)**	**< 1 year - 5mg** **1- 2 years - 7.5mg** **2 -3 years - 10mg** **> 3 years - 12.5mg**
NHL 902 **COPADM 1,2,3,** **COP/CYM** **NHL 903** **COPADM 1,2,3** **COP, CYM** **CYT/ETOP**	**< 1 year - 5mg** **1- 2 years - 7.5mg** **2 -3 years - 10mg** **> 3 years - 12.5mg** **Note 2^{o} or 3^{o} THERAPY WITH IT ARA-C / HYDROCORTISONE**
BABY BRAIN **(CNS 9204)**	**NOT APPLICABLE**
UKALL R1	**1 year - 7.5mg** **2 years - 10mg** **> 3 years - 12.5mg**
NHL FAB/LMB 96	**< 1 year - 8 mg** **1-2 years - 10 mg** **2-3 years - 12 mg** **> 3 years - 15 mg** **Triple therapy with cytosine/hydrocortisone**

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