PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

HIGH DOSE METHOTREXATE OVERVIEW LEUKAEMIA / LYMPHOMA

PROTOCOL REF: MPHAHDMHA
(Version No. 2.0)

Approved for use in:

- Treatment of acute lymphoblastic leukaemia (Intensification phase)
- Treatment or prophylaxis of CNS lymphoma
- Treatment of high grade lymphoma

This protocol should be used in conjunction with specific treatment protocols as an administration guide for the high dose methotrexate component of these treatments

Blueteq not required

Regimens:

Protocol	Dose	Route	Duration
UKALL 14	**3g/m^2**	IV infusion	3 hours, 15 minutes
UKALL 60+	**1g/m^2**	IV infusion	3 hours, 15 minutes
CNS Prophylaxis	**3.5g/m^2**	IV infusion	3 hours, 15 minutes
MATRIX	**3.5g/m^2**	IV infusion	3 hours, 15 minutes
RMP	**3g/m^2**	IV infusion	3 hours, 15 minutes
R-CODOX-M	**3g/m^2**	IV infusion	3 hours, 15 minutes
LYASPMEDEX	**3g/m^2**	IV infusion	3 hours, 15 minutes

Maximum dose to be given over 3 hours 15 minutes is 3.5g/m^2
Please refer to trial protocol for any other regimens such as UKALL 2011 (5g/m^2)

There are 4 key elements that are required to be prescribed, supplied and administered in order to ensure high dose methotrexate is given safely and appropriately that are common to all treatment protocols:

1. Sodium Bicarbonate

- Methotrexate infusion can only begin when urinary pH is > 7. The pH must be maintained >7 during treatment until methotrexate has cleared (level < 0.1µmol/L).
- The pre-methotrexate hydration fluids detailed below require 50mL sodium bicarbonate 8.4% (50mmol) to be added to commercial fluid bags (1000mL sodium chloride 0.18% & glucose 4% with 0.15% (20mmol) potassium chloride). This should maintain alkaline urinary pH.
- Urinary pH should be monitored before every bag change and whenever possible during methotrexate treatment
- Oral sodium bicarbonate (1g QDS) must be administered starting 24 hours before methotrexate and should continue until methotrexate level < 0.1µmol/L, to support alkaline urinary pH. If urinary pH <7 during methotrexate infusion then additional sodium bicarbonate 8.4% 50mL can be infused separately by slow IV infusion (to be prescribed PRN in Meditech).

2. Hydration Fluids

- Patients must receive continuous hydration fluids whilst being treated with high dose methotrexate. This must commence 6 hours before treatment starts and continue until the methotrexate has cleared (level < 0.1µmol/L). Ideally hydration should be started in the early hours of the morning (3-4am) so that high dose methotrexate can start at 10am (ideally during the morning) in order for subsequent levels can be taken and reported within working hours.
- Hydration fluid must be prescribed on pre-printed hydration proforma.

- The standard hydration fluid is 1000mL sodium chloride 0.18% & glucose 4% with 0.15% (20mmol) potassium chloride with 50mmol sodium bicarbonate (bicarbonate added at ward level).
- Each 1000mL bag is given at a rate of 250mL/hr, reduced to 125mL/hr whilst methotrexate is being administered.
- Patient's fluid balance should be checked 4hourly (prior to each bag change). Escalate to medical staff if signs of fluid overload and consider oral or intravenous furosemide therapy (20-40mg).

3. Folinic acid (Calcium folinate):

- Folinic acid is vital for the safe removal of methotrexate from the circulation after a high dose infusion. This is started **intravenously** 24 hours after the **start** of the methotrexate infusion at a dose of 60mg QDS until the methotrexate level is < 0.1µmol/L. See methotrexate level monitoring section for dose escalation advice.
- High dose methotrexate **MUST NOT** be administered without IV folinic acid present at ward level. Nursing staff must check this prior to initiating methotrexate infusion.

4. Methotrexate Level Monitoring:

- A methotrexate level should be taken **48 hours** after the **start** of the infusion and sent directly to the Alder Hey lab as urgent (taxi booked by ward staff). Subsequent levels should be taken daily thereafter until the methotrexate has cleared (< 0.1µmol/L). Ideally high dose methotrexate should be started at 10am (or during the morning) so that subsequent levels can be taken at 10am each day and be reported and reviewed within working hours.
- Nursing staff should contact Alder Hey lab if level not reported within a few hours. **All levels reported should be documented in the clinical notes.**
- Nursing staff must review the level with the table below to determine if any further action required. Contact a Haematology Consultant if:

- Any methotrexate level above 0.5µmol/L as an increased calcium folinate dose is required.
- Serum creatinine increases by more than 25% from baseline as the folinic acid rescue should be escalated even before MTX level is known.
- If severe methotrexate toxicity is suspected.

Methotrexate level (µmol/L)	Dose of calcium folinate (folinic acid)
> 1	200mg/m^2 IV every 6 hours
0.5 – 0.99	100mg/m^2 IV every 6 hours
0.3 – 0.49	60mg IV every 6 hours
< 0.3	30mg PO every 6 hours

Glucarpidase can be considered for urgent treatment of methotrexate-induced renal dysfunction in patients who have:

- received high dose (> 1g/m^2) methotrexate
- optimised supportive measures including the use of fluids and folinic acid
- significant deterioration in renal function (serum creatinine > 1.5 x ULN or oliguria)
- toxic plasma methotrexate levels

Refer to CCC Glucarpidase protocol for further information

Emetogenic risk:

See individual protocols

Supportive treatments:

Prescribe on regimen specific pre-printed prescription proforma)

- Hydration fluids to start at least 6 hours before methotrexate

Prescribe the following as inpatient medication in Meditech:

- Sodium bicarbonate 1g PO four times daily from 24 hours pre-methotrexate
- Sodium bicarbonate 8.4% 50mL (50mmol) IV infusion prn (to be administered if urinary pH <7)

- Folinic acid IV 60mg every 6 hours to start 24 hours after the *start* of methotrexate infusion
- Pentamidine NEB 300mg every 28 days (salbutamol 5mg NEB to be given immediately prior to pentamidine) OR atovaquone liquid PO 750mg BD
- Other supportive medication detailed in protocol (antimicrobials, mouthwash, steroids etc)
- Famotidine 20mg twice daily (if on existing PPI therapy, not needed routinely)
- Ensure co-trimoxazole is stopped 2 days prior to methotrexate infusion
- Ensure routine folic acid supplements stopped prior to methotrexate infusion. Can re-start once methotrexate level <0.1µmol/L.

Extravasation risk:

Methotrexate: non-vesicant

Refer to the CCC policy for the 'Prevention and Management of Extravasation Injuries'

Dosing in renal and hepatic impairment:

A fluid space, e.g. pleural effusion or ascites, is potentially very dangerous as methotrexate can accumulate and cause prolonged toxicity. High dose methotrexate should not be given in such cases.

Methotrexate			
Renal (ml/min) – use wright equation			
>60		100% dose	
40-60		50%	
<40		Omit	
Hepatic			
Bilirubin (micromol/L)		ALT (units/L)	Dose modification
<50	And	<180	100% dose
50-84	Or	≥180	75% dose
≥85			Omit

Interactions:

- Concomitant administration of NSAIDs and methotrexate at high doses has reportedly elevated and prolonged serum methotrexate levels, resulting in deaths from severe haematological and gastrointestinal toxicity
- Penicillins can reduce renal clearance of methotrexate. Haematological and gastrointestinal toxicity have been observed in combination with high and low dose methotrexate.
- Trimethoprim/sulfamethoxazole (co-trimoxazole) has reportedly increased myelosuppression in patients treated with methotrexate, probably due to reduced tubular secretion and/or an additive antifolate effect.
- Care is required with drugs that also cause renal and hepatic impairment
- Methotrexate can reduce clearance of theophylline. Theophylline levels must therefore be monitored during concomitant treatment with methotrexate.
- Vitamin preparations containing folic acid or its derivatives can cause a reduced response to systemically administered methotrexate, however conditions in which there is a deficiency of folic acid can increase the risk of methotrexate toxicity
- Literature data indicate that co-administration of proton pump inhibitors and methotrexate, especially at high dose, may result in elevated and prolonged plasma levels of methotrexate and/or its metabolite, possibly leading to methotrexate toxicity.

Treatment schedule:

See individual protocols.

Main toxicities:

Bone marrow suppression, mucositis, stomatitis, nausea, vomiting, diarrhoea, skin irritation.

Glucarpidase – Methotrexate reversal agent

NHS England will fund glucarpidase as a reversal agent for methotrexate (unlicensed in UK) for adults receiving high-dose methotrexate chemotherapy (doses >1g/m^2)

- Who develop significant deterioration in renal function (>1.5x ULN and rising, or the presence of oliguria) OR
- Have toxic plasma methotrexate level AND
- Have been treated with all standard rescue and supportive measures AND
- At risk of life-threatening methotrexate-induced toxicities

The recommended dose is one single intravenous injection of 50units/kg

Refer to CCC glucarpidase protocol for further information

References:

1. Mckay, P.; Wilson, M.; Chaganti, S.; Smith, J.; Fox, C. P.; Cwynarski, K. The prevention of central nervous system relapse in diffuse large B-cell lymphoma: a British Society for Haematology good practice paper. British Journal of Haematology. 2020;190(5):708-714.
2. UKALL 14. A randomised trial for adults with newly diagnosed acute lymphoblastic leukaemia. UCL. Protocol version 12. 2018
3. UKALL 60+. A phase 2 study for older adults with acute lymphoblastic leukaemia. UCL. Protocol version 4. 2016
4. Summary of Product Charceteristics for Voraxaze. March 2013 (FDA)
5. Wright GFR Equation Calculator. Available from: https://www.mdapp.co/wright-gfr-equation-calculator-584/ [accessed 1st March 2021]

Circulation/Dissemination

Date added into Q-Pulse	8th June 2023
Date document posted on the Intranet	N/A

Version History

Date	Version	Author name and designation	Summary of main changes
	1.0	**Mark Nelson**	New protocol
April 2023	2.0	**Jennifer Gibson**	**Transferred to new template. Protocol review.**