

HIGH DOSE METHOTREXATE AND FOLINIC ACID RESCUE (UKALL I4 PROTOCOL)

INDICATIONS: ALL, high grade lymphoma

Since methotrexate is excreted by the kidneys renal function must be closely monitored before, during and after treatment and doses must be modified if renal function is impaired. In high doses methotrexate may precipitate in the renal tubules leading to renal failure. This is minimised by maintaining a high fluid throughput, urinary alkalinisation and monitoring of plasma methotrexate levels. Liaise closely with oncology pharmacist and nursing staff re-timing of methotrexate infusion, the hydration regimen and blood sampling for methotrexate levels.

Prior to treatment

- Patients must not receive cotrimoxazole in the week prior to methotrexate.
- Check LFTs prior to each cycle – methotrexate may be contraindicated if there is significant liver dysfunction. *Discuss with consultant.*
- Check FBC prior to each cycle; Neuts must be >1.0 and platelets >100 before starting. Delay for up to 2 weeks and consider use of GCSF. If levels are not reached it may be appropriate to proceed with 50% dose – *discuss with consultant.* Note that bone marrow infiltration may be responsible for delayed haematological recovery from methotrexate.
- Before 1st and 3rd methotrexate infusions check GFR by creatinine clearance. The initial GFR must be >100 ml/hr and must be >50 ml/hr prior to the 3rd cycle. If there is any doubt delay treatment and repeat GFR. If methotrexate excretion is delayed after the first cycle, repeat GFR prior to the second.
- If GFR shows impaired renal function – *discuss with consultant.* Note recommendations in UKALL XII for methotrexate dose modifications in case of impaired renal function before 2nd and 3rd cycles are:

GFR >50 ml/min	no dose modification necessary
GFR 10-50ml/min	use 50% dose
GFR <10 ml/min	do not give methotrexate
- Methotrexate may accumulate in effusions leading to delayed excretion and haematological toxicity – drain pleural effusions and ascites before starting
- Review the use of nephrotoxic drugs or other drugs which may interact with methotrexate before starting, including NSAIDs (delay renal tubular secretion)
- High dose methotrexate must be used with extreme caution in the presence of peptic ulceration or ulcerative colitis.
- A urinary pH >7.0 must be recorded before starting the methotrexate infusion.
- If appropriate discuss possibility of pregnancy with female patients and need for contraception with both male and female patients. Discuss risk of infertility - offer semen cryopreservation to males
- Central venous access should be established before commencing high dose methotrexate – preferably in the form of a double lumen Hickman line
- Written consent

High dose methotrexate infusion schedule

To minimise the risks of haematological and nephrotoxicity give hydration and folinic acid as below and check plasma methotrexate level every 24hrs starting at 48hrs from the start of the methotrexate infusion. Monitoring can be discontinued when the patient has been 'rescued' i.e plasma methotrexate level is $0.1\mu\text{mol/l}$

T minus 6 hrs	<ul style="list-style-type: none"> Commence pre-hydration with dextrose-0.45% saline with 50mmol NaHCO_3 and 20mmol KCl in each litre at $125\text{ml/m}^2/\text{hour}^*$ <p><i>Monitor urine pH by urinalysis or send to biochemistry if in doubt</i></p>
T = 0 hrs	<ul style="list-style-type: none"> Methotrexate 300mg/m^2 in 100ml normal saline over 1 hour Write up the first dose of folinic acid to be given at T +36hrs Continue hydration fluid as above
T + 1hr	<ul style="list-style-type: none"> Methotrexate 2.7g/m^2 in 1.0L normal saline over 23 hours Continue hydration fluid as above through the other arm of a Y extension set* Adjust infusion rates so the combined rate is $125\text{ml/m}^2/\text{hour}$
T + 24hrs	<ul style="list-style-type: none"> Stop methotrexate infusion even if not completed for any reason Continue hydration fluid as above at $125\text{ml/m}^2/\text{hour}$ for a minimum of 48 hours
T =36-48hrs	<ul style="list-style-type: none"> IV folinic acid 15mg/m^2 every 3 hours <p>The doses at 36, 39, 42 and 45 hrs should be prescribed as 4 stat doses on the front of the drug chart. The doses at 36 & 39 hrs should be IV; the doses at 42 & 45 should be either IV or oral – the oral route can be used if the patient is not vomiting</p>
T = 48hrs	<ul style="list-style-type: none"> Send serum sample to biochemistry for 48hr plasma methotrexate level Continue folinic acid 15mg/m^2 every 6 hrs – this should be prescribed on the regular section of the drug chart If patient does not suffer nausea or vomiting, iv hydration can be reduced or stopped but ensure that a combined fluid intake of $3\text{L/m}^2/24\text{hrs}$ is maintained If 48hr methotrexate level $< 0.1\mu\text{mol/l}$ 'rescue' has been completed, folinic acid and fluids may be discontinued If MTX level at 48 hrs is between 0.1 & $20\mu\text{mol/l}$, continue folinic acid 15mg/m^2 every 6 hrs If methotrexate level is $> 20\mu\text{mol/l}$ – need to discuss with Consultant, as need to increase dosing of folinic acid as per UKALL 14 trial protocol on S drive
T = 72hrs	<ul style="list-style-type: none"> Send sample to biochemistry for 72hr plasma methotrexate level (brown top tube) Continue folinic acid and fluid intake as above If 72hr methotrexate level $< 0.1\mu\text{mol/l}$ 'rescue' has been completed, folinic acid and fluids may be discontinued If MTX level at 72 hrs is between 0.1 & $2\mu\text{mol/l}$, continue folinic acid at 15mg/m^2 every 6 hrs If methotrexate level is $> 2\mu\text{mol/l}$ - need to discuss with Consultant, as need to increase dosing of folinic acid as per UKALL 14 trial protocol on S drive
T = 96hrs	<ul style="list-style-type: none"> Continue to send samples for plasma methotrexate level every 24 hours Maintain fluid intake and folinic acid until 'rescue' has occurred, i.e level $< 0.1\mu\text{mol/l}$ The dose of folinic acid only needs increasing if the level at any time point after 72 hrs is $> 2\mu\text{mol/l}$ <p>* Hydration fluid is prepared by pharmacy with the above concentrations of KCl and NaHCO_3 in 3.0L bags</p>

During methotrexate infusion and folinic acid rescue:

- Continue to ensure urine pH is > 7 by giving stat doses of 3.0g NaHCO₃ orally
- Check daily U&Es, creatinine and alternate day FBC, LFTs
- Monitor fluid balance carefully and give iv frusemide if fluid overload occurs or urine output falls to <400ml/m² in any 4-hour period.
- Note that plasma methotrexate levels are performed by the Biochemistry Dept, Christie Hospital, Manchester, Tel: 0161-446-3298. If they receive the sample before 2pm the result will be available the same day

Following methotrexate infusion and folinic acid rescue

- Check FBC, U&Es, creat, LFTs at least twice during the week following the first and second cycles to detect any delayed toxicity that may occur.

High Dose Methotrexate Toxicities

Neutropenic sepsis & thrombocytopenia	Nephrotoxicity
Diarrhoea, gastrointestinal ulceration and bleeding	Hepatotoxicity (acute transaminitis)
Amenorrhoea & infertility (offer semen cryopreservation)	Stomatitis
Acute pulmonary toxicity (fever, cough, interstitial infiltrates)	Rash

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