Guidelines for use of HIGH DOSE METHOTREXATE (HDMTX):

Overview:
Protocols using high dose methotrexate (>1g/m²) differ in terms of dose, duration of infusion, methotrexate assessment time points and final methotrexate (MTX) target levels. However similar principles apply to ensure safe levels which fall appropriately.

High dose methotrexate (HDMTX) can lead to significant nephrotoxicity (4%) and neurotoxicity.

To avoid serious complications and “out of hours” results the following guidance should be adhered to:

- Discuss MTX and creatinine levels with senior staff member, incorrect management of patients is potentially life threatening

- DO NOT co-prescribe the following medicines which reduce MTX excretion: NSAIDS, ciprofloxacin, co-trimoxazole, penicillin, probenecid, omeprazole, piperacillin- tazobactam (this list is not exhaustive – please check for drug interactions). AVOID NEPHROTOXIC DRUGS.

- ASSESS AND DOCUMENT THE PATIENT’S BASELINE CREATININE prior to starting hydration

- Start fluids for hydration the evening before the MTX infusion is due, and run overnight

- If creatinine on admission slightly higher than usual repeat creatinine level must be taken just before the MTX infusion starts

- Aim to start the HDMTX infusion during the early part of the day; 9 am – midday so that the results of levels are back in working hours and adjustments to hydration, folinic acid rescue, etc. can be made by the ward (rather than on call) team.

- Serum creatinine must be measured with each MTX level, it will usually be back before the MTX level and allows the earlier detection of any possible problems and earlier intervention

- The key time points for MTX measurement are protocol dependent

- All MTX levels are expressed as micromolar per litre (µmol/l or µM)
Overview of malignancies which use HDMTX:

1. **ACUTE LYMPHOBLASTIC LEUKAEMIA/LYMPHOMA:**
   
   Check protocols/guidance for ALL, Relapsed ALL, Infant ALL and Philadelphia positive ALL

2. **NON – HODGKIN LYMPHOMA:**
   
   Check B – NHL protocol or guidance for Anaplastic Large Cell Lymphoma

3. **OSTEOSARCOMA (trial closed)**
   
   Check Appendix B in EURAMOS (closed trial) protocol or open trial

4. **INFANT EPENDYMOMA (trial closed)**
   
   Check Appendix B in Infant Ependymoma (closed trial) or open trial protocol

5. **Headstart II (Infant Medulloblastoma)**
   
   Rescue as B – NHL Guidelines for Group C patients

**INDICATIONS FOR GLUCARPIDASE (CARBOXYPEPTIDASE/VORAXAZE):**

If appropriate rescue with increased folinic acid and hydration is unsuccessful and the patient develops methotrexate induced renal dysfunction, glucarpidase should be considered (this MUST be a consultant decision)

**Indications for use are:**

1. Renal dysfunction following MTX administration
2. Significant MTX toxicity because of significantly delayed excretion

**Pointers to possible use:**

1. Creatinine >2 x baseline (100% increase) by 24 hours
2. Raised MTX levels and poor urine output despite 200ml/m²/hr and diuretic support
3. Check protocols for specific indications
4. Prolonged excretion and reduced clearance because of renal dysfunction
Glucarpidase is an orphan medicine and is not licensed in the UK, therefore can only be ordered on a named patient basis.

Glucarpidase reduces the MTX levels by >98% within 15 minutes of administration.

It is a recombinant form of the bacterial enzyme carboxypeptidase G2, and works by rapidly hydrolyzing methotrexate into inactive non cytotoxic metabolites. These are not eliminated by the kidney, providing an alternative clearance route in patients who have acute kidney injury and delayed renal elimination.

Glucarpidase is incredibly expensive and is not kept as stock as OUH, however is available for dispatch 24hours/ day, 365 days per year.

- Dose = 50 units/kg as a STAT dose intravenously
- 2 x 1000unit vial costs £26,280* (prices correct at time of publication (April 2015)
- For patients <40kg, a STAT dose costs £26,280
- For patients >40kg, a STAT dose costs £52,560

Glucarpidase is clinically commissioned for the urgent treatment of methotrexate-induced renal dysfunction. The NHS England clinical commissioning policy can be accessed [here](#).

If the patient doesn’t meet the criteria defined in the clinical commissioning policy, then an urgent IFR (refer to the procedure on the Paediatric Haematology Oncology Homepages) must be submitted and approval from the Chair of the Medicines Management and Therapeutics Committee (MMTC) must be sought only after discussion with a Haem/Onc Consultant

**PROCEDURE FOR ARRANGING VORAXAZE®:**

- Inform Senior Staff Member If meets clinical commissioning criteria , then consultant prescribes Voraxaze® (glucarpidase)
- If it doesn’t meet the clinical commissioning criteria, then the consultant must complete and urgent IFR and request approval from Chair of MMTC.
- Consultant completes patient access form (available via the Paediatric Haematology Oncology Homepages under Pharmacy/ Pharmacy Links)
- Contact Paediatric Haem/Onc Pharmacist/ Pharmacist on – call (ensure that pharmacy are aware of the dose being prescribed)
- If orders out of hours, inform the oncall pharmacist that the “out of hours ordering information is available on the available via the Paediatric Haematology Oncology Homepages under Pharmacy/ Pharmacy Links
- Pharmacist to contact Clinigen to arrange supply
ADMINISTRATION OF GLUCARPIDASE:

- Maintaining alkalinisation of urine with sodium bicarbonate is essential to maintain urinary pH>7.
- Stop Folinic acid 2 hours before administering glucarpidase as it is a competitive substrate and may compete with MTX for glucarpidase binding sites.
- Folinic acid should not be administered in the 2 hours prior to or the 2 hours following the administration of glucarpidase.
- Dose of glucarpidase: 50 units/kg administered by intravenous bolus over 5 minutes (flush line pre and post dose with a compatible fluid).
- Estimation of Methotrexate concentrations after the administration of glucarpidase is unreliable as metabolites interact with the MTX assay, therefore use creatinine as a guide for efficacy. Continue therapy with folinic acid rescue until the serum creatinine has been maintained at an acceptable level for a minimum of 3 days.
- For 48 hours after glucarpidase administration, determine the folinic acid dose based on the patient’s pre-glucarpidase methotrexate concentration.
- Continue hydration and alkalinisation of the urine as indicated.
- For further drug/administration information, the manufacturer’s Summary of Product Characteristics (SPC) for glucarpidase is available via the Paediatric Haematology Oncology Homepages under Pharmacy/Pharmacy Links.

References:

2. Green JM. Glucarpidase to combat toxic levels of methotrexate in patients. Therapeutic and Clinical Risk Management (2012); 8: 403 – 413
## Review

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