Clinical Guideline

SAFE USE OF HIGH DOSE METHOTREXATE IN PAEDIATRICS

SETTING
Starlight Ward and Apollo 35, Bristol Royal Hospital for Children

FOR STAFF
Medical, nursing and pharmacy staff in the above settings.

PATIENTS
Paediatric patients receiving high dose methotrexate.

Attention

The administration of High Dose Methotrexate (HDMTX) carries a significant potential toxicity which in extreme cases can be fatal. This is prevented by effective Folinic Acid Rescue (FAR).

Absolute compliance with the schedule of hydration, monitoring of levels and FAR is mandatory to ensure the safe administration of HDMTX.

It is vital to read the chemotherapy protocol fully before prescribing and commencing administration of HDMTX. Please also ensure that you have made certain that your patient has no contraindications to HDMTX as detailed in this document.

Contents

Section | Page
--- | ---
1. Indications for practice | 2
2. Authorised personnel/training required | 2
3. Procedure | 2
   3.1 PLANNED ADMISSION | 3
   3.2 PRE-ADMINISTRATION CHECKLIST | 3
   3.3 URINARY pH AND URINE OUTPUT | 4
   3.4 PRE-HYDRATION | 4
   3.5 DOSAGE AND INFUSION TIME | 4
   3.6 POST-HYDRATION | 4
   3.7 FOLINIC ACID (CALCIUM FOLINATE/LEUCOVORIN) RESCUE | 4
   3.8 MONITORING AND INTERPRETING MTX LEVELS | 4
   3.9 HIGH METHOTREXATE LEVELS | 5
   3.10 GLUCARPIDASE (carboxypeptidase) | 5
   3.11 HYPERTRANSAMINASEMIA AND HYPERBILIRUBINEMIA | 6
4. HDMTX- significant drug interactions | 6

References and further information | 7
1. **Indications for practice**

1.1 HDMTX is used in a range of cancer treatment protocols for children and young people.

1.2 HDMTX has a serious toxicity profile with potential for pharmacokinetic and pharmacodynamic drug interactions. Its excretion can be inhibited by certain drugs, it is extensively protein bound and may be displaced by certain drugs and there is an increased risk of severe bone marrow depression if administered with other drugs that can suppress the activity of dihydrofolate reductase. Regular drug levels and Folinic Acid Rescue (FAR) are required during administration.

1.3 Different chemotherapy protocols mandate different durations of administration, timing of FAR and timing of MTX level checks.

1.4 Prior to starting HDMTX therapy, pre-administration checks should be completed as detailed on the FAR sheet. The FAR sheet can be found on the DMS.

1.5 MTX is a folate antagonist and limits DNA and RNA synthesis by inhibiting dihydrofolate reductase and thymidylate synthase. This mechanism is responsible for both its therapeutic and toxic effects.

1.6 MTX is excreted almost entirely by the kidneys and therefore good renal function and alkalisation of urine with a pH ≥ 7 is vital to avoid toxicity. Most is excreted within 48 hours unchanged in the urine but there is considerable variation amongst patients. Toxicity depends more on the duration of exposure than on the dose administered.

1.7 Following high dose intravenous treatment, plasma levels are predictive of toxicity and therefore HDMTX containing protocols have detailed information to be followed in order to reduce the risk of toxicity.

2. **Authorised personnel/training required**

2.1 HDMTX can be prescribed by a qualified doctor/non-medical prescriber (NMP) deemed competent to prescribe Systemic Anti-Cancer Therapy (SACT).

2.2 HDMTX can be administered by any member of qualified nursing staff who has been assessed as competent in administering IV drugs with appropriate chemotherapy training.

3. **Procedure**

   Always check protocol-specific guidance during each step of MTX administration and rescue.

   MTX levels must be reviewed against Protocol-specific guidance by chemotherapy-trained medical staff and this documented prior to stopping hydration and FAR.
3.1 PLANNED ADMISSION

- All HDMTX due to start on day 1 should have a planned admission to Starlight ward or Apollo 35 the day before treatment to start hydration overnight. For patients on the A2G trial fluids should be commenced at 02:00am.
- On admission the patient should be reviewed and signed as ‘fit’ to go ahead, chemotherapy authorised, and drug chart completed.
- If HDMTX is not on day 1, pre-hydration should be commenced overnight or started in the early hours of the morning. The methotrexate infusion should start between the hours of 10:00-11:00.
- MTX should ideally be made by the Parenteral Services Unit (PSU) and delivered to the ward the day before administration, or be ready by 10:00 on the day of infusion.

All of the above is to ensure timings and reviews of the MTX levels are completed within daytime hours.

3.2 PRE-ADMINISTRATION CHECKLIST

Prior to starting HDMTX the following checklist should be completed by the admitting doctor or nursing staff:

<table>
<thead>
<tr>
<th>TASK</th>
<th>RESPONSIBILITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Copy of relevant SACT flow sheet in notes.</td>
<td>Primary check- In chemo prescribing</td>
</tr>
<tr>
<td>Medication prior to admission reviewed and appropriate medicines stopped</td>
<td>Second check- Admitting SpR/ Nursing staff/ Pharmacy staff</td>
</tr>
<tr>
<td>Alert sticker added to drug chart to state patient on HDMTX and to avoid interacting drugs</td>
<td>Admitting SpR/ NMP/ Pharmacy staff</td>
</tr>
<tr>
<td>Patient reviewed &amp; weight checked. Check patient does not have diarrhoea or pleural effusions</td>
<td>Prescribing Doctor in ‘FIT’ for clinic/Admitting SpR/ NMP/Pharmacy staff</td>
</tr>
<tr>
<td>Bloods are reviewed according to protocol. Creatinine is assessed against the patient’s admission baseline.</td>
<td>Prescribing Doctor in ‘FIT’ for clinic/Admitting SpR/NMP/Pharmacy/ Nursing staff</td>
</tr>
<tr>
<td>Chemotherapy Authorised on ChemoCare</td>
<td>Prescribing Doctor in ‘FIT’ for clinic/SpR/NMP/ Second check-Nursing staff</td>
</tr>
<tr>
<td>Central Venous line in situ and working</td>
<td>Nursing staff</td>
</tr>
<tr>
<td>FAR available on ward</td>
<td>Pharmacy/Nursing staff</td>
</tr>
<tr>
<td>FAR Sheet available</td>
<td>Nursing staff</td>
</tr>
<tr>
<td>Urine pH ≥7 before starting</td>
<td>Nursing staff to inform Doctor/ANP</td>
</tr>
</tbody>
</table>
### 3.3 URINARY pH AND URINE OUTPUT

Hydration (with sodium bicarbonate containing infusions) throughout treatment is essential until FAR is no longer required and final MTX level is achieved as per protocol.

On commencement of hydration every urine must be collected, and the pH checked and documented on the fluid chart until the patient has cleared the MTX and FAR completed. Urinary pH must be maintained at ≥7 throughout the period of treatment to ensure optimal methotrexate excretion. A drop in pH must be urgently communicated to the patient’s medical team. If 50mmol sodium bicarbonate/litre is insufficient to keep the urine pH ≥7, refer to the patient’s chemotherapy protocol for guidance.

*Nursing staff must inform doctor/ANP of pH value before starting MTX infusion*

### 3.4 PRE-HYDRATION

Varies between protocols- see specific protocol.

### 3.5 DOSAGE AND INFUSION TIME

This varies between protocols- see specific protocol. If MTX infusion does not stop at prescribed time, there is a risk of life threatening toxicities. Note, even if the infusion is not complete at this point, it must be stopped.

For protocols where the first 10% of the dose is administered separately to the subsequent 90%, the infusion line after the 10% bag has completed should be flushed using the 90% bag. A volume to be infused (VTBI) of 25mls should be inputted into the pump at the same rate of the 10% dose. Once this has completed the rate prescribed for the 90% bag should be inputted into the pump and started.

### 3.6 POST-HYDRATION

Varies between different protocols-see specific protocol.

### 3.7 FOLINIC ACID (CALCIUM FOLINATE/LEUCOVORIN) RESCUE (FAR)

Folinic acid will be prescribed on ChemoCare.

Check the protocol carefully and complete a FAR sheet. If FAR is delayed or stopped too early there is a risk of life-threatening toxicities, and if continued too long it can reduce therapeutic effect of HDMTX.
The FAR sheet can be accessed on the DMS via the following link:

3.8 MONITORING AND INTERPRETING MTX LEVELS

Each protocol gives specific guidance when to check the MTX levels and will advise if a
dose change for FAR is necessary- please read the protocol carefully.
Contact the ward doctor immediately if levels are out of range.

Monitor renal and liver function daily.

3.9 HIGH METHOTREXATE LEVELS\textsuperscript{1,4,6}

Elevated plasma concentrations of MTX can lead to life threatening toxicities e.g. Acute
kidney injury (AKI), myelosuppression, hepatitis and other toxicities including mucositis
and dermatitis.

If the patient is following a trial protocol (either on or “off trial”) follow the guidance for
high levels in the trial protocol for increasing FAR doses and hydration.

3.10 GLUCARPIDASE\textsuperscript{4,5,6,7} (carboxypeptidase)

Glucarpidase is a reversal agent (unlicensed in the UK) which may be considered for
patients with toxic MTX levels. It is an orphan drug, so only available on a named patient
basis. The cost is in excess of £50,000 for a single dose. NHS England will fund

\textbf{Glucarpidase for patients receiving HDMTX doses (defined as >1g/m}^2)\textbf{ who:}

1. Develop significant deterioration in renal function (serum creatinine > 1.5 Upper
   Limit of Normal (ULN) and rising or oliguria)
2. Have toxic plasma MTX levels (note defining a toxic MTX level is complicated by
   the regimen used and the time at which the level is tested).\textsuperscript{3}
3. Have been treated with all standard rescue and supportive measures AND are at
   risk of life threatening MTX-induced toxicities.

The decision to use glucarpidase must always be approved by a consultant
haematologist or oncologist.

For full commissioning policy see
treatment-of-methotrexate-induced-renal-dysfunction.pdf

MTX levels following administration of glucarpidase:

Glucarpidase reduces methotrexate levels by >98% within 15 minutes.

\textbf{NOTE}: Samples taken within 48 hours of administration of glucarpidase will be unreliable
for determining methotrexate levels. Glucarpidase hydrolyses the C-terminal glutamate
of methotrexate to form the inactive metabolite DAMPA and glutamate. Because DAMPA
is structurally very similar to methotrexate it cross reacts with the methotrexate antibody in the assay. As a consequence, this assay will underestimate the impact of glucarpidase on methotrexate concentrations initially as the values will be falsely high.

**Do not administer folinic acid for 2 hours before and after glucarpidase administration (as per licensed information- US).**

For the first 48 hours post administration of glucarpidase continue the same dose of folinic acid rescue given prior to glucarpidase then continue until methotrexate levels <0.1 micromol/L for a minimum of 3 days.

Continue hydration and alkalisation of the urine as indicated

**Glucarpidase dosing:** 50 Units/kg as a single dose (all ages).

Administration: Slow intravenous injection over 5 minutes.

For full prescribing and administration information consult SPC available at [https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125327lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125327lbl.pdf)

**Glucarpidase supply:** Glucarpidase is not stocked at UH Bristol; it is made in the US (but stock held centrally in the UK) and needs to be ordered on a named patient basis.

*Within working hours* – Contact ward pharmacist.

*Out of hours* – Contact emergency duty pharmacist via switch.

### 3.11 HYPERTRANSAMINASEMIA AND HYPERBILIRUBINEMIA

It is expected that patients receiving HDMTX will develop hypertransaminasemia and/or hyperbilirubinemia. These elevations can last up to two weeks following HDMTX infusion.

### 4. HDMTX- significant drug interactions

An alert should be added to drug chart for all patients receiving HDMTX stating that they are on high dose MTX as part of their current SACT regime and to avoid the following drugs during HDMTX treatment:

1. Penicillins (including combination agents such as co-amoxiclav or piperacillin/tazobactam- Tazocin)
2. Trimethoprim (including Co-trimoxazole*)
3. Non-Steroidal Anti-Inflammatory Drugs
4. Ciprofloxacin
5. Probenecid
6. Proton pump inhibitors e.g., Omeprazole
7. Tetracyclines
8. Any renal toxic drug such as Gentamicin or Vancomycin
*For paediatric patients only on the ALLTogether1 Trial co-trimoxazole is continued throughout all treatment phases but should be avoided on the day of MTX administration—see trial protocol.

Be cautious when prescribing ANY nephrotoxic drugs (including gentamicin) or hepatotoxic drugs.

**REFERENCE**

2. FOLINIC ACID SPC- accessed via: [https://www.medicines.org.uk/emc/product/1296](https://www.medicines.org.uk/emc/product/1296)
4. VORAXAZE SPC-accessed via: [https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125327lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/125327lbl.pdf)
5. Voraxaze (glucarpidase) dosing information accessed via [www.voraxaze.com](http://www.voraxaze.com)

**RELATED DOCUMENTS AND PAGES**

- FAR record sheets
- [Methotrexate nursing infusion sticker](#) on DMS – (Links to this are also found on the Starlight ward, Apollo 35 and BRHC Oncology, Haematology and BMT Services workspaces)

**AUTHORISATION**

- Paediatric Haematology, Oncology and Bone Marrow Transplant Quality Assurance Forum (Quaf)

**SAFETY**

- No safety concerns in addition to those already stated (see page 1)

**QUERIES AND CONTACT**

- Haematology registrar bleep 3495
- Oncology registrar bleep 2950
- Pharmacist bleep 2731.
- Out of hours – Contact emergency duty pharmacist via switchboard.