High dose METHOTREXATE

[High grade NHL CNS prophylaxis]

INDICATION

Licensed / NHSE funded: **HIGH GRADE NON-HODGKIN LYMPHOMA (NHL) WITH HIGH RISK OF CENTRAL NERVOUS SYSTEM (CNS) INVOLVEMENT** [ICD-10 codes: C82-84]

Definition of high-risk disease for diffuse large B-cell lymphoma (DLBCL) is a score 5 or 6 based on the following risk factors:

- Age > 60
- Raised serum LDH
- Stage III or IV
- Performance status > 1
- Multiple extranodal sites (2 or more)
- Renal or adrenal involvement

In addition, the following extranodal sites are deemed high risk:

- Testes
- Breast
- Renal or adrenal

NB. The following sites are NOT deemed high risk: tonsil, isolated bone marrow involvement, epidural, cranio-facial involvement unless erosion through base of skull.

Use with caution in patients over 70 years of age, and/or with significant co-morbidities.

TREATMENT INTENT

CNS prophylaxis alongside a curative regimen

PRE-ASSESSMENT

1. Blood tests - FBC, U&Es, LDH, ESR, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, HbA1c, Igs, β2 microglobulin, hepatitis B core antibody and hepatitis B surface antigen, hepatitis C antibody, EBV, CMV, VZV, HIV, HTLV-1, glucose 6-phosphate dehydrogenase (G6PD) when indicated [H.8], group and save.
2. Assess **renal function** (Wright GFR) and the risk of methotrexate (MTX) nephrotoxicity. Consider directly measuring GFR (NM GFR), using, for example, ^{99m}Tc-DTPA to assess baseline renal function, especially in patients with pre-existing renal impairment, extremes of body weight and other co-morbidities. When it is impractical to obtain NM GFR and / or GFR is < 80mL/min, discuss MTX dose with Consultant and the benefits versus risks of proceeding with treatment. If off-label use is required, follow appropriate Trust governance processes [see DOSE MODIFICATIONS below].
3. Assess any pathologic **fluid accumulation (third space fluids) such as ascites or pleural effusions** that may lead to prolonged methotrexate plasma elimination and unexpected toxicity. High dose methotrexate should not be given in such cases, and therefore pleural effusions and ascites should be drained prior to initiation of methotrexate treatment.
4. Confirm **medication history** and check for any **drugs** that can inhibit renal tubular secretion of MTX. These mainly include co-trimoxazole, penicillins, aspirin, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) and Proton Pump Inhibitors (PPIs). Counsel patients to **stop co-trimoxazole** in the week before the first high dose methotrexate (MTX) infusion. If Pneumocystis jirovecii pneumonia (PJP) prophylaxis is required, switch to pentamidine as an alternative. Co-trimoxazole can be restarted after the last cycle of high dose MTX, once the MTX level is below 0.1 micromol/L and adequate neutrophil count recovery is achieved.

   NSAIDs, PPIs and penicillin antibiotics should also be avoided during methotrexate infusion.

Tazocin should **NOT** be used during high dose methotrexate administration or rescue – use an alternative as per local formulary and antibiotic guidelines. Review indications for aspirin, NSAIDs and PPIs and consider stopping during methotrexate treatment and prescribing alternative if required (see DRUG INTERACTIONS below).

5. Assess **cardiac function**, ECG +/- ECHO - if clinically indicated.
6. Record performance status [ECOG].
7. Record vital signs, height and weight.
8. Urine pregnancy test - before cycle 1 of each new chemotherapy course for women of child-bearing age unless they are post-menopausal, have been sterilised or had a hysterectomy.
9. Consent and counselling - ensure patient has received adequate verbal and written information regarding their disease, treatment and potential side effects. **Advise patients to take precautions in the sun to avoid photosensitivity reactions** [MHRA Drug Safety Update]. Document in medical notes all information that has been given. Obtain written consent on the day of treatment.
10. Fertility - it is very important the patient understands the potential risk of infertility; all patients should be offered fertility advice by referring to the Oxford Fertility Unit.
11. Assess and document tumour lysis syndrome (TLS) risk as part of pre-assessment. Patients should be adequately hydrated before and after each cycle administration. In bulky disease pre-hydrate with sodium chloride 0.9% 1 litre over 4-6 hours. Refer to the TLS protocol [H.8].
12. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
13. Start hydration and urine alkalinization with sodium bicarbonate at T= -12 hours. T= 0 is the start time of the methotrexate infusion (see DRUG REGIMEN below). Dipstick urine every 2 hours to check pH is maintained ≥ 7. **If pH < 7, give additional sodium bicarbonate as required.** Review regular sodium bicarbonate requirements at the end of the methotrexate infusion, and continue as appropriate until methotrexate level is < 0.1 micromol/L.
14. Methotrexate infusion should be administered over 3 hours 15 minutes, although it may be extended if technical issues restrict the flow rate.
15. Intrathecal chemotherapy is **NOT** a part of this regimen.
16. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Day(s)	Time [hrs]	Drug	Dose	Route	Administration details
0	–12	Hydration & urine alkalinization pre-Methotrexate			See **Table 1**, page 3
1	**0**	**METHOTREXATE**	**300 mg/m²**	IV	First dose of MTX: in exactly 100mL sodium chloride 0.9% **over 15 minutes**
1	**0**	**METHOTREXATE**	**2700 mg/m²**	IV	Second dose of MTX (commence immediately after the first dose): in exactly 500mL sodium chloride 0.9% **over 3 hours**
1	+3	Hydration & urine alkalinization post-Methotrexate			See **Table 1**, page 3
2	+24	Calcium folinate (folinic acid) post-Methotrexate			See **Table 1**, page 3
CYCLE FREQUENCY: 21 days					
DURATION: 2 – 4 cycles *					

* Normally 2 cycles of intravenous methotrexate would be administered, after a full course of R-CHOP chemotherapy (typically 6 cycles). R-CHOP chemotherapy should not be interrupted for administration of IV methotrexate (unless for intravascular DLBCL). 2–4 doses of intrathecal methotrexate may also form part of the CNS prophylaxis regimen in particular high-risk cases such as testicular lymphoma, to be administered with the first few cycles of R-CHOP (or equivalent chemotherapy).

Table 1. High-dose Methotrexate (HD MTX) toxicities prophylaxis and management

<table>
<tr><td>Pre-hydration and urine alkalinization</td><td>
▪ Start 12 hours before methotrexate (MTX) infusion.
▪ IV continuous infusion: 1000 mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 100 mmol. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m^2). Duration: continuous infusion for 15 hours 15 minutes (run concurrently with the MTX infusion). PO: Sodium bicarbonate 1500 mg four times daily + 1500 mg 2-hourly when required.
▪ Dipstick urine every 2 hours to check if pH ≥ 7. If pH under 7, give additional sodium bicarbonate (PO) 1500 mg.
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<tr><td>Urine output</td><td>
▪ Check every 4 hours. Aim: 400 mL/m^2/4 hours (approximately 700 mL over 4 hours). Furosemide: Administer 20-40 mg when required to maintain urine output.
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<tr><td>Post-hydration and urine alkalinization</td><td>
▪ Start immediately at the end of MTX infusion.
▪ IV continuous infusion: 1000 mL Glucose 2.5%, sodium chloride 0.45% with potassium chloride 20 mmol and sodium bicarbonate 50 mmol. Flow rate: 200 mL/hour (or 150 mL/hour if BSA less than 1.6 m^2). Duration: continuous infusion until MTX level < 0.1 µmol/L. PO: Sodium bicarbonate 1500 mg four times daily + 1500 mg 2-hourly when required.
▪ Dipstick urine every 2 hours to check if pH ≥ 7. If pH under 7, give additional sodium bicarbonate (PO) 1500 mg.
▪ Review the need for regular sodium bicarbonate at the end of MTX infusion and continue as appropriate until MTX levels < 0.1 µmol/L.
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<tr><td>Calcium folinate (folinic acid)</td><td>
▪ Start 24 hours after the start of MTX infusion: 15 mg/m^2 IV every 3 hours for 5 doses, then 15 mg/m^2 IV/PO* every 6 hours until MTX levels < 0.1 µmol/L.
▪ Based on plasma MTX levels and after discussing with the Consultant, calcium folinate dose may need adjustment as below.
<table>
<tr><th colspan="4">Calcium folinate (folinic acid) dose
according to plasma MTX levels after 48 hours from the start of MTX infusion</th></tr>
<tr><th>Plasma MTX level</th><th>< 0.5 µmol/L</th><th>0.5–1 µmol/L</th><th>> 1 µmol/L</th></tr>
<tr><td>Calcium folinate dose</td><td>15 mg/m^2 IV/PO*
every 6 hours</td><td>50 mg/m^2 IV
every 6 hours</td><td>100 mg/m^2 IV
every 6 hours</td></tr>
</table>
* PO tablets may only be given if the patient is not nauseous/vomiting and dose is ≤ 30 mg as the tablet bioavailability greatly decreases with the higher doses.
▪ Calcium folinate 100 mg/m^2 IV 6 hourly should also be administered in patients with toxic plasma MTX levels > 20 µmol/L after 24 hours or until the MTX level is known following MTX overdose, or in patients with clinical features of MTX toxicity (e.g. mucositis, signs of bone marrow suppression, hepatotoxicity or renal dysfunction).
▪ Due to the large quantities of calcium, the infusion time of calcium folinate at doses > 200–500 mg (or the patient's body surface area (BSA) × 50) should be over 1–2 hours. Monitor calcium concentrations closely.
</td></tr>
<tr><td>Glucarpidase</td><td>
▪ Consider early glucarpidase in MTX induced renal dysfunction (> 1.5 x baseline and rising, or the presence of oliguria) and presence of toxic plasma MTX levels: > 20 µmol/L after 24 hours or > 5 µmol/L after 48 hours from the start of MTX infusion, despite rescue measures, which might be life-threatening.
▪ Administration of glucarpidase should optimally occur within 60 hours from the start of MTX infusion, because life-threatening toxicities may not be preventable beyond this time point. Clinical data however show that glucarpidase continues to be effective beyond this time window. Folinic acid should not be administered within 2 hours before or after glucarpidase administration to minimise any potential interaction. In the absence of more specific HPLC assay, the dose of folinic acid used in a 48 hour-period after glucarpidase should be based on the MTX concentration from a sample taken prior to glucarpidase administration.
▪ The recommended dose is one single intravenous injection of 50 units/kg. Multiple doses are not permitted. Blueteq required. Refer to [NHSE Glucarpidase policy] and [TVCA Glucarpidase guideline] for more details.
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</table>

CONCURRENT MEDICATIONS

Hydration and urine alkalinization pre-& post-MTX / Calcium folinate – see **Table 1**, page 3.	
Antiviral prophylaxis	Aciclovir 200mg TDS during treatment and for 3 months after completion
Anti-emetics Day 1: Moderate risk	▪ Ondansetron on day 1: 8mg BD ▪ Metoclopramide on days 1-4: 10-20mg TDS. For breakthrough nausea or vomiting: 10-20mg TDS when required. For alternative options, refer to [TVCA Anti-emetic guideline].
Gastric protection*	Consider Famotidine 20mg twice daily [avoid PPIs – see INTERACTIONS below]
PJP prophylaxis*	Consider Pentamidine 4mg/kg IV infusion once a month (max. 300mg) [avoid co-trimoxazole – see INTERACTIONS below]

(*) indicates optional concurrent medications

CONTRAINDICATIONS

Refer to individual Summary of Product Characteristics (SmPC) for full details. Leptomeningeal involvement, severe active infection, hypersensitivity to drugs in the regimen. High-dose MTX: renal impairment [see DOSE MODIFICATIONS below], severe liver impairment, ascites or pleural effusions.

INVESTIGATIONS

- FBC, U&Es, LFTs, magnesium, calcium, phosphate, urea
- Weight, vital signs, pH to maintain ≥ 7.
- Plasma **MTX levels** starting **from 24 hours after the start of MTX infusion**, then **every 24 hours.**
- CXR as clinically indicated.

RESTAGING

On completion of 2 cycles of HD MTX

DOSE MODIFICATIONS

All dose modifications must be discussed with the Consultant.

- **Dose reduction of MTX should be considered in patients > 70 years** due to reduced liver and kidney function, as well as lower folate reserves that may be associated with the increased age.

Haematological toxicities
Proceed with each cycle only if neutrophils > 1.0 x 10^9/L and platelets > 75 x 10^9/L.

Non-haematological toxicities	
Grade 3 or 4 toxicities	Discuss with Consultant – next cycle should be delayed until toxicity grade is ≤ 2

Renal / Hepatic Impairment

GFR (Glomerular Filtration Rate) = estimated using Wright formula (Wright GFR), or measured using isotopic filtration markers, for example, ^{99m}Tc-DTPA or ^{51}Cr-EDTA (NM GFR).

NM GFR [uncorrected] should be considered at extremes of body weight and based on individual patient clinical context (age, co-morbidities). When impractical to obtain NM GFR, discuss alternative methods to assess renal function with the Consultant.

	Renal impairment	Hepatic impairment
Methotrexate	GFR ≥ 80 mL/min: 100% dose GFR 50-79 mL/min: 100% dose, or consider dose reduction (see below*) GFR < 50 mL/min: omit	Mild and moderate: caution required, consider dose reduction or discontinue with concomitant renal impairment or constant increase in liver enzymes – clinical decision (see below**) Severe: avoid use

* Discuss with the Consultant whether to proceed with a full dose to maintain dose intensity for optimal treatment outcomes, or consider dose reduction in individual patients, especially those with poorer performance status and/or co-morbidities. Consult Nephrology when appropriate. Note off-label use when a full dose is administered for GFR < 80 mL/min and any dose for GFR < 60 mL/min (refer to SmPC for full details). If off-label use is required, follow the appropriate Trust governance processes. If dose reduction is required, it will apply to the second MTX dose only in a cycle (administered over 3 hours).

** Patients receiving high dose methotrexate may develop hypertransaminasemia and occasionally hyperbilirubinemia. These elevations can last up to 2 weeks following the methotrexate infusion and are not considered toxicity requiring discontinuation of repeated administration of methotrexate. Persistent hyperbilirubinemia and/or grade 3-4 hypertransaminasemia for longer than 3 weeks should result in discontinuation of the drug.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- **Methotrexate:** renal damage, hepatotoxicity, interstitial pneumonitis (cough, dyspnoea, fever), stomatitis, diarrhoea, skin changes and increased skin sensitivity to sun, gritty eyes, hair loss, neurotoxicty including headache, dizziness, blurred vision and loss of balance.

Photosensitivity reactions – refer to [MHRA advice for healthcare professionals]

- Known side effect of MTX that can occur with both low-dose and high-dose treatment.
- Reactions manifest as severe sunburn such as rashes with papules or blistering, with some patients reporting swelling; rarely, photosensitivity reactions contributed to deaths from secondary infections.
- Healthcare professionals, including those prescribing and dispensing methotrexate: remind patients to take precautions to protect themselves from the sun and UV rays. Suspected adverse drug reactions associated with MTX should be reported via [MHRA Yellow Card].

DRUG INTERACTIONS

Co-trimoxazole	Avoid concomitant use. Acute megaloblastic pancytopenia, probably due to additive inhibition of the dihydrofolic acid reductase can occur. Co-trimoxazole should be stopped a week before the start of methotrexate (MTX) and held until methotrexate levels < 0.1micromol/L and neutrophil count recovery.
Penicillins	Avoid concomitant use. Reduced renal clearance of MTX can occur. Tazocin (piperacillin with tazobactam) should NOT be used until MTX level < 0.1 micromol/L – use an alternative as per local formulary and antibiotic guidelines.
NSAIDs and salicylates	Avoid concomitant use. Severe (including fatal) bone marrow suppression, aplastic anaemia and gastrointestinal toxicity have been reported with concomitant administration of MTX (usually in high dosage).
PPIs	Avoid concomitant use. Delayed elimination and increased serum MTX can occur.
Antidiabetic agents	Insulin-dependent diabetes should be carefully monitored because liver cirrhosis and an increase in transaminases can occur.

EXTRAVASATION RISK

Methotrexate: inflammatory agent

TREATMENT RELATED MORTALITY

< 1%

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REVIEW

Name	Revision	Date	Version	Review date
Cheuk-kie Jackie Cheung, Haematology Pharmacist	Removal of fluconazole in line with other first line DLBCL regimen	Dec 2019	1.6	May 2020
NSSG Lymphoma Group	Annual protocol review	Aug 2020	1.7	May 2022
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, NSSG Lymphoma Group	Dose modifications, contraindications, interactions, and references sections updated. Annual protocol review. General formatting.	July 2022	2.0	July 2024
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist NSSG Lymphoma & CLL Group	Pre-assessment, adverse reactions & interactions updated. MHRA advice on photosensitivity reactions added. Drug regimen: MTX split dose included to increase CNS penetration. MTX toxicity prophylaxis and management [calcium folinate and glucarpidase advice updated; timing to check first MTX levels amended to 24 hours post MTX infusion]. Concurrent medications: anti-emetics added. MTX dose modifications (renal impairment) and references updated. General formatting. Annual protocol review.	September 2024	3.0	September 2026
		January 2025	3.1	September 2026