Methotrexate ORAL

INDICATION

Licensed / NHSE funded: **LARGE GRANULAR LYMPHOCYTE (LGL) LEUKAEMIA** [ICD-10 code: C91]

Refer to protocol [L.141] for Langerhans cell histiocytosis (LCH) indication.

TREATMENT INTENT

Disease modification

PRE-ASSESSMENT

1. Ensure histology is confirmed prior to administration of chemotherapy and document in notes.
2. Blood tests - FBC, ESR, U&Es, LDH, urate, calcium, vitamin D level, magnesium, creatinine, LFTs, glucose, Igs, β_2 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.
3. Assess **renal function** (Wright GFR) and risk of methotrexate (MTX) nephrotoxicity. Caution should be exercised if there is significant renal impairment as its use may result in accumulation/toxicity with additional renal damage (see TREATMENT MODIFICATIONS below).
4. 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 (for example, myelosuppression). Pleural effusions and ascites should be drained before methotrexate is started.
5. 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.
6. ECG +/- ECHO - if clinically indicated.
7. Chest X-ray at baseline.
8. Record performance status [ECOG].
9. Record vital signs, height and weight.
10. 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 prior to treatment.
11. **Pre-cycle 1:** short course of steroids or granulocyte colony-stimulating factor (G-CSF) can be considered to support cytopenias prior to MTX treatment – discuss with the Consultant.
12. Fertility - it is very important the patient understands the potential risk of reduced fertility. All patients should be offered fertility advice by referring to the Oxford Fertility Unit.
13. Assess and document tumour lysis risk as part of pre-assessment. Refer to the Tumour Lysis Syndrome in Adults protocol [H.8].
14. Advise dental check is carried out by patient's own dental practitioner before treatment starts.
15. Treatment should be agreed in the relevant MDT.

DRUG REGIMEN

Day(s)	Drug	Dose	Frequency	Route	Administration details
1, 8, 15,22	**METHOTREXATE (MTX)**	***10 mg/m^2**	**ONCE WEEKLY (Mondays)**	PO	Dispensed as 2.5mg tablets. Swallow whole with plenty of water. Oral liquid (off-label use) is an option for difficulty swallowing / enteral feeding.
CYCLE FREQUENCY: 28 days					
TREATMENT DURATION: until disease progression or unacceptable toxicity					

*** Maintenance cycles:** consider MTX at a lower dose, for example 5 mg/m^2.

CONCURRENT MEDICATIONS

Antiviral prophylaxis	Aciclovir 200mg TDS during treatment and for 3 months after completion
Folate supplement	**FOLIC ACID 5mg ONCE WEEKLY (Fridays)** Note: Patients can be advised to take **M**ethotrexate on **M**ondays and **F**olic acid on **F**ridays to aid memory. Alternatively, folic acid 5mg twice-weekly can be considered (not to be taken on the day of MTX).
TLS prophylaxis*	Minimal risk: no routine prophylaxis required
Antiemetics*	Minimal emetic risk: no routine prophylaxis required

(*) indicates optional concurrent medications

CONTRAINDICATIONS

Hypersensitivity to active ingredients and excipients. Active severe infections. Severe renal and hepatic impairment. Refer for full details to the Summary of Product Characteristics (SmPCs).

INVESTIGATIONS

Every 4–6 weeks FBC, LFT, U&E, creatinine prior to dosing.
CXR should be performed at baseline and if chest symptoms develop.

RESTAGING

Continue for at least 4 months as treatment effect may be delayed.

TREATMENT MODIFICATIONS

Haematological toxicities:

- If neutrophil count < 1 x 10^9/L or platelets < 100 x 10^9/L, consider delaying treatment by one week unless due to disease related cytopenia.

Non-haematological toxicities:

- For grade ≥ 3 non-haematological toxicities, delay treatment until the adverse effect has resolved to grade ≤ 1. Consider dose reductions – discuss with the Consultant.

Renal impairment	GFR ≥ 60 mL/min: 100% dose GFR 30-59 mL/min: 50% dose GFR < 30 mL/min: not recommended
Hepatic impairment	Mild and moderate impairment: Cycle 1: 100% dose. Monitor closely for early signs of toxicity – delay or adjust dose as needed at the Consultant discretion. Severe impairment: not recommended

DRUG INTERACTIONS

Avoid concomitant use	Sulfamethoxazole and folate antagonists (trimethoprim, co-trimoxazole) (increased risk of haematological toxicity), retinoids (acitretin), general anaesthesia (nitrous oxide), other hepato-, hemato- or nephrotoxics.
Considerable caution required	MTX dose should be monitored with concomitant use of aspirin, ibuprofen or indometacin. Concomitant use of high-dose MTX and NSAIDs has been associated with fatal MTX toxicity. If risk factors such as renal function disorders, including mild renal impairment, are present, combined administration with NSAIDs is not recommended. Dehydration may also intensify the toxicity of MTX.
Caution required	Increased risk of MTX toxicity with acidic anti-inflammatories, salicylates, phenytoin, barbiturates, tranquilisers, oral contraceptives, p-aminobenzoic acid, amidopyrine derivatives, thiazide diuretics, doxorubicin, tetracyclines, probenecid, sulfinpyrazone, oral hypoglycaemics, omeprazole (avoid with high dose MTX). Phenytoin (risk of exacerbation of convulsions). Vitamins or other products containing folic acid, or its derivatives may impair methotrexate efficacy.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

- > 10%: bone marrow suppression, infections (respiratory, cutaneous, bacterial), mucositis (dose-dependent), gastrointestinal problems (diarrhoea, bleeding), renal failure, nausea and vomiting
- 1-10%: skin rash, hepatic toxicity, pulmonary toxicity (interstitial pneumonitis)

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 methotrexate should be reported via [MHRA Yellow Card].

TREATMENT RELATED MORTALITY

< 1%

REFERENCES

1. Fox CP, Ahearne MJ, Pettengell R, Dearden CE, El-Sharkawi D, Kassam S, Cook L, Cwynarski K, Illidge T, Collins G. Guidelines for the management of mature T-and natural killer-cell lymphomas (excluding cutaneous T-cell lymphoma): a British Society for Haematology Guideline. British Journal of Haematology| BJH. 2022 Feb;196(3):507-22.
2. Pfizer Limited. Maxtrex 2.5 mg Tablets. Summary of Product Characteristics (SmPC). Last updated 06/02/2024. Available at https://products.mhra.gov.uk/ <Last accessed 17/09/2024>
3. British Oncology Pharmacy Association. Administration of oral systemic anticancer therapy (SACT) via enteral feeding tubes and other methods: Guidance on the use of oral SACT for patients unable to swallow. Version 2.0. 06/09/2023.

REVIEW

Name	Revision	Date	Version	Review date
NSSG Lymphoma Group	Annual protocol review	May 2017	1.4	
NSSG Lymphoma Group	Annual protocol review	May 2019	1.5	May 2021
NSSG Lymphoma Group	Update to concurrent meds	May 2020	1.6	May 2021
Natalia Czub, Advanced Haematology Pharmacist, Dr Graham Collins, Consultant Haematologist, NSSG Lymphoma & CLL Group	Pre-assessment, drug regimen, dose modifications, adverse reactions, references updated. MHRA advice on photosensitivity reactions added. Concurrent medications (folic acid, aciclovir included), interactions, contraindications added. General formatting. Annual Protocol review.	September 2024	2.0	September 2027