PROTOCOL

The Clatterbridge Cancer Centre NHS Foundation Trust

Systemic Anti Cancer Therapy Protocol

Oral or Subcutaneous Weekly Methotrexate Large Granular Lymphocytic Leukaemia And Cutaneous T-cell Lymphoma

PROTOCOL REF: MPHAOSWM
(Version No. 1.0)

Approved for use in:

- Large granular lymphocytic leukaemia in patients with significant cytopenias and a PS 0 to 2.
- Cutaneous T-Cell Lymphoma
- No Blueteq needed

Dosage:

Drug	Dose	Route	Frequency
Methotrexate	**10mg/m^2**	Oral	Once a week on the same day every week. Titrate dose to blood counts
OR Methotrexate	**10mg/m^2**	Sub cutaneous injection	Once a week on the same day every week Titrate dose to blood counts

Continue until disease progression or unacceptable side effects

Administration:

- Methotrexate must be given once a week ONLY for this indication
- If a patient is not tolerating oral methotrexate due to gastrointestinal side effects then a trial of subcutaneous methotrexate could be considered
- In CCC methotrexate tablets are only available in a 2.5mg strength so the dose must be in multiples of 2.5mg

- Subcutaneous methotrexate is available in 7.5mg, 10mg, 12.5mg, 15mg, 17.5mg, 20mg, 22.5mg, 25mg, 27.5mg and 30mg pre-filled syringes.
- The patients receiving subcutaneous methotrexate will need to be trained in the administration (or a district nurse) and a cytotoxic sharps container.
- Prolonged treatment (3-6 months) is often necessary to achieve a response and responders usually require long term maintenance

Emetogenic risk:

Mildly emetogenic

Supportive treatments:

- Allopurinol PO 300mg OD for first cycle only (100mg OD if CrCl is < 20ml/min)
- Metoclopramide PO 10mg TDS prn
- Folic acid PO 5mg OD between once a week and six times a week as specified by consultant. Folic acid should *not* be taken on the same day as methotrexate.

Interactions:

Methotrexate is immunosuppressive and may therefore reduce immunological response to concurrent vaccination. Severe antigenic reactions may occur if a live vaccine is given concurrently.

General anaesthesia – nitrous oxide increases the antifolate effect of methotrexate (increased frequency of stomatitis and myelosupression).

Antipsychotics – increased risk of agranulocytosis with olanzapine.

Retinoids – plasma concentrations of methotrexate increased by acitretin – also increased risk of hepatotoxicity.

Azopropazone – excretion of methotrexate reduced.

Sulfamethoxazole and folate antagonists such as trimethoprim (as co-trimoxazole) – increased risk of haematological toxicity.

Probenecid & weak organic acids (e.g. loop diuretics: pyrazoles) - excretion of methotrexate reduced (increased risk of toxicity).

NSAIDs – In animals low doses of methotrexate with NSAIDs have been found to decrease the tubular secretion of methotrexate and possibly to increase its toxicity. However patients with rheumatoid arthritis (or psoriasis) have been treated concurrently with methotrexate 7.5 - 15 mg/week without significant problems.

Aspirin and other salicylates - possible alteration of the pharmacokinetics of methotrexate/increased risk of toxicity.

Neomycin (and possibly tetracycline, chloramphenicol: non-absorbable broad spectrum antibiotics) – reduced absorption of methotrexate

Ciprofloxacin – excretion of methotrexate possibly reduced (increased risk of toxicity)

Doxycycline, sulphonamides, tetracyclines - increased risk of methotrexate toxicity

Penicillin – reduced excretion of methotrexate - increased risk of toxicity (hematological and gastrointestinal).

Antifolate effect of methotrexate increased by phenytoin

Phenytoin – absorption possible decreased by cytotoxics (risk of exacerbation of convulsions)

Enzyme-inducing antiepileptics – increased/altered metabolism and/or clearance of methotrexate

Carbamazepine, phenytoin and valproate serum levels can be reduced by antineoplastic drugs with seizures if the antiepileptic doses are not raised appropriately.

Pyrimethamine – increased anti-folate effect of methotrexate.

Digoxin absorption decreased by cytotoxics.

Ciclosporin -increased risk of toxicity.

Corticosteroids- increased risk of haematological toxicity.

Leflunomide – risk of toxicity.

Theophylline -methotrexate possibly increases plasma concentrations of theophylline.

Omeprazole and pantoprazole – excretion of methotrexate possibly reduced (increased risk of toxicity).

Vitamin preparations containing folic acid or its derivatives may change response to methotrexate.

Triamterene - bone marrow suppression and reduced folate concentrations have been reported when triamterene and methotrexate were co-administered.

Oral hypoglycaemics – possible reduced methotrexate excretion.

Thiazide diuretics – possible reduced methotrexate excretion.

The concurrent administration of agents such as p-aminobenzoic acid and sulfinpyrazone will decrease the methotrexate transport function of renal tubules, thereby reducing excretion and almost certainly increasing methotrexate toxicity.

Main toxicities:

Thrombocytopenia, neutropenia, anaemia, nausea, vomiting, diarrhoea, mucositis, dizziness and fatigue

Investigations and treatment plan:

	Pre	Cycle 1	Cycle 2	Cycle 3	Ongoing
Informed Consent	X				
Clinical Assessment	X			X	As clinically indicated or at the end of treatment
SACT Assessment (to include PS and toxicities)	X	X	X	X	Every cycle
On treatment review					
FBC	X	X	X	X	Every cycle
U&E & LFTs & Magnesium	X	X	X	X	Every Cycle
CrCl (Cockcroft and Gault)	X	X	X	X	Every cycle
CT scan	X				Only if clinically indicated
Bone marrow biopsy	X				Repeat as clinically indicated
ECG					If clinically indicated
Blood pressure measurement	X				Repeat if clinically indicated
Respiratory Rate					If clinically indicated
Weight recorded	X	X	X	X	Every cycle
Blood glucose	X				Repeat if clinically indicated

Dose Modifications and Toxicity Management:

Haematological toxicity:

For LGL leukemia the first cycle should proceed despite any cytopenias. Furthermore because cytopenias are a feature of the disease which can take up to six months to respond no dose adjustments or suspensions should be made unless the cytopenia is new.

Proceed if (but see note above)-

ANC ≥ 1.0 x 10^9/L	Plt ≥ 75 x 10^9/L

Neutrophils can be supported by GCSF if required.

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological toxicity:

Dosing in renal and hepatic impairment:

Renal	For CrCl between 20-50ml/min consider starting at a lower dose and titrating carefully. Not recommended inpatients with a CrCl <20ml/min.

Hepatic	Bilirubin >86micromols/L not recommended

References:

1. https://www.medicines.org.uk/emc methotrexate 2.5mg tablets revised 07/01/2020; accessed 27/05/2022
2. https://www.medicines.org.uk/emc Metoject 10mg pre-filled syringe revised 18/09/2019; accessed 27/05/2022

3. Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Oncol 2019;20: e201–08.
4. Fox C.P. et al. Guidelines for the Management of Mature T-cell and NK-cell Neoplasms (Excluding cutaneous T-cell Lymphoma): a British Society for Haematology Guideline Updated Nov 2021 https://onlinelibrary.wiley.com/doi/full/10.1111/bjh.17951

Circulation/Dissemination

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Version History

Date	Version	Author name and designation	Summary of main changes
July 2022	1.0	**Aileen McCaughey** **Advanced Pharmacist Haemato-oncology- NMP**	New Regimen Protocol