PHARMACY TREATMENT PROTOCOL

Oral Methotrexate for Use in Immune Mediated Conditions

PROTOCOL REF: MPHAMETHIM
(Version: 1.0)

Indication:

Treatment of patients with severe immune-related adverse events which do not/ incompletely respond to corticosteroids and require additional immunosuppression, the most common of which will be the treatment of immunotherapy induced arthralgia.

Methotrexate should only be used by clinicians that are familiar with the various characteristics of the drug and its mode of action.

Patients should be referred for review by the appropriate medical specialty, following the initiation of methotrexate.

Treatment must be prescribed by a Systemic Anti-Cancer Therapy (SACT) approved registrar or consultant

Exclusion Criteria for Methotrexate

- Current sepsis or infection
- Ascites or significant pleural effusion
    - Systemic toxicity of methotrexate may be enhanced in patients with ascites or other effusions due to prolongation of the serum half-life. Pleural effusions and ascites should be drained prior to initiation of methotrexate therapy.
- Immunodeficiency syndromes
- Severe / significant renal impairment

  - Methotrexate should be used with caution in patients with renal impairment. See guidance below

- Significant hepatic impairment
  - Methotrexate should be used with caution, if at all, in patients with significant current or previous liver disease, especially if due to alcohol. See guidance below.
- Liver disease including fibrosis, cirrhosis, recent or active hepatitis
- Serious cases of anaemia, leucopenia or thrombocytopenia
- Pregnancy or breastfeeding

Dosage:

Drug	Dosage	Route	Frequency
Methotrexate	15mg	PO	Once weekly on the same day each week for 2 weeks
	20mg	PO	Once weekly on the same day each week after initial 2 week treatment

Supportive treatments:

Folic acid should be given at a dose of 5mg ONCE daily except the day of methotrexate as standard.

The prescribing and supply of methotrexate for these patients should ONLY be by The Clatterbridge Cancer Centre NHS foundation Trust (CCC). Shared care is NOT suitable.

Initiation:

Before prescribing methotrexate, it is the responsibility of the prescriber to ensure that:

1. The patient has been counseled and received the NPSA booklet which describes the benefits and risks of methotrexate. The booklet also acts as an information and recording diary in which patients can store all information about their administration routine, notes to discuss with clinicians, and their monitoring blood test results. Please ensure patient details on page 1 are filled out appropriately.
2. That the indication fits the clinical situation

In-patient prescribing:

When prescribing methotrexate for an in-patient it is the responsibility of the prescriber to ensure that:

1. Methotrexate is prescribed **WEEKLY**
2. When prescribing on an inpatient chart, that the 6 days of the week when methotrexate is not being administered are crossed out.
3. Folic acid is prescribed daily alongside the methotrexate except on the day of the week when methotrexate is being taken.
4. The patient is clinically suitable for the treatment

Out-patient prescribing:

When prescribing methotrexate it is the responsibility of the prescriber to ensure that:

1. Methotrexate is prescribed **WEEKLY**
2. The patient is clinically suitable for the treatment
3. Folic acid is prescribed daily alongside the methotrexate except on the day of the week when methotrexate is being taken.
4. Initially only 2 weeks supply of methotrexate is to be prescribed then a maximum of 4 weeks can be prescribed thereafter.

Pharmacy supply:

Pharmacy will ONLY keep and supply the **2.5mg** methotrexate tablets as per NPSA guidance to reduce any dispensing errors with different strengths.

When supplying methotrexate, it is the responsibility of the healthcare professional dispensing the medication to ensure that:

1. The label on the dispensed medication states the number of tablets to take in addition to the total dose in milligrams. (E.g. Take SIX tablets (15mg) ONCE weekly)
2. The patient has received counselling and the information/monitoring booklet. Please check to ensure the booklet is being filled in appropriately. (E.g. blood results, dosage changes).

3. If the patient has not been counselled to run through the main counselling points below.

Counselling:

1. Methotrexate is taken WEEKLY on the same day each week. Advise patient to document their 'day of the week' to take methotrexate on page 17 of their monitoring booklet.
2. If folic acid is also prescribed, advise patients NOT to take folic acid on the same day as methotrexate.
3. Advise patients to take methotrexate with food if they experience nausea if it's currently being taken on an empty stomach.
4. Advise patients on missed doses (see page 4 of NPSA patient booklet)
5. Advise patients to avoid self-medication with over the counter NSAID's (e.g. aspirin or ibuprofen)
6. Advise patients to speak to their doctor, pharmacist or nurse if they experience :
    - Nausea, upset stomach or diarrhoea
    - Mouth ulcers, sore throat or sore mouth
    - Infections
    - Rashes
    - Thinning of hair
7. Advise patients to stop methotrexate and seek urgent medical advice if signs suggestive of:
    - Blood disorders (e.g. severe sore throat, bruising, bleeding and severe mouth ulcers)
    - Liver toxicity (e.g. nausea, vomiting, abdominal discomfort and dark urine, jaundice)
    - Respiratory effects (e.g. shortness of breath)
    - Severe and continuing diarrhoea or vomiting
    - Pregnancy
    - Chickenpox and shingles

8. Counsel patient on bringing their purple booklet to their clinic appointments for their doctor to fill in their dose and blood results (this should be checked by the pharmacist in PharmaC prior to dispensing)

Monitoring:

Test	Frequency
Chest X-ray	Before treatment is started unless the patient has had a CT scan within the past 8 weeks.
Full Blood Count	Before treatment is started and every week for the first 8 weeks after which, if bloods stable, monitoring can be undertaken monthly until cessation
Renal Function	
Hepatic Function	

Note – If the treatment is long term (i.e. 6 months or longer) the medical team may decide to perform monitoring tests at longer intervals (i.e. every 2-3 months).

At each monitoring appointment please ensure:

1. Any blood tests are recorded on page 21 of the patients NPSA booklet. If monitoring is conducted over the phone then patients are encouraged to complete this themselves during review.
2. Any dose changes are recorded on page 19 of the patients NPSA booklet

Main Toxicities:

For severe reactions, discuss with Consultant before continuing with treatment.

Side effect	Management
WBC < $4x10^9$/L	Perform a differential and increase frequency of monitoring
WBC < $3.5x10^9$/L	Withhold and discuss with a specialist. Bone marrow suppression can occur abruptly.
Neutrophils < $2.0x10^9$/L	Withhold and discuss with a specialist. Bone marrow suppression can occur abruptly.
Platelets < $150x10^9$/L	Withhold and discuss with a specialist. Bone marrow suppression can occur abruptly.
MCV > 105 -110 fl	Check folate, B_{12} and TFTs, and treat if appropriate. If WBC normal repeat in 4 weeks.
MCV > 110 fl	Stop methotrexate and seek advice.
Nausea and/or vomiting	Usually improves over time. If troublesome consider: • Continue folic acid 6 days a week omitting on the day

	methotrexate is taken • Splitting methotrexate dose over one evening and next morning. • A short-term anti-emetic.
Hair loss	Usually mild, rarely significant. Reversible on stopping methotrexate.
Rash	Withhold treatment and discuss with a specialist.
Mouth ulcers, mucositis	Mouth ulcers may respond to folic acid. If severe despite extra folic acid, stop methotrexate and refer to a specialist for advice.
Menstrual dysfunction/amenorrhoea	May occur during treatment and for a short while after cessation.
Otherwise unexplained dyspnea or cough	Methotrexate pneumonitis may occur. Withhold treatment, arrange chest CT (HRCT) and CXR and discuss urgently with consultant.
Abnormal bruising	Withhold until FBC result is available.
Sore throat or other unusual infection	Urgent FBC and withhold until FBC result is available. Susceptible to opportunistic infections such as viral wart, TB and pneumocystis.
Cervical dysplasia	Regular cervical smears
Diarrhoea	Consider reducing dose
Fever, chills	Withhold until FBC result is available
Stomatitis	Withdraw treatment

Use in elderly

Methotrexate should be used with extreme caution in elderly patients, a dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves which occurs with increased age.

Renal impairment

- Reduce dose in renal impairment. Avoid in severe impairment.
- Methotrexate is excreted to a significant extent by the kidneys therefore renal impairment affects the clearance of methotrexate.
- Patients who develop dehydration, pre-renal or acute renal failure while on methotrexate should have methotrexate withheld and FBC monitored closely. Review any changes in medication particularly ACEIs and ARBs.

Creatinine clearance (mL/min)	Dose
>50	100%
20 to 50	50%
<20	**HOLD**

Hepatic impairment

Avoid in severe hepatic impairment.

Liver cirrhosis reported. Treatment should not be started or should be discontinued if any abnormality of liver function tests or liver biopsy is present or develops during therapy. Abnormalities can return to normal within 2 weeks after which treatment may be recommenced if judged appropriate.

Parameter	Advice
Bilirubin level >85.5 µmol/L	Withhold dose
>2 fold rise in ALT or AST	Withhold and discuss with a specialist.
Unexplained fall in albumin	Withhold and speak to specialist.

Vaccinations

Live vaccines should NOT be used whilst on Methotrexate

Inactive vaccines (including the IM seasonal flu vaccine and pneumococcal vaccine) are safe for use whilst on methotrexate

Methotrexate has some immunosuppressive activity and therefore the immunological response to concurrent vaccination may be decreased. In addition, concomitant use of a live vaccine could cause severe antigenic reaction.

Interactions

Agent	Advice
Alcohol	Should be reduced as much as possible. One unit of alcohol per day may be sanctioned.
Anticonvulsant	Monitor anticonvulsant levels
Antimalarial	Anti-folate effect of methotrexate increased by pyrimethamine (Fansidar, Daraprim)
Antipsychotic	Avoid concomitant use with clozapine (increased risk of agranulocytosis)
Ciprofloxacin	Monitor – as excretion of methotrexate may be reduced with use of this drug, giving rise to an increased risk of toxicity
Phenytoin / Theophylline	Avoid concomitant use as methotrexate levels may be increased.
Corticosteroids	Methotrexate may have a 'steroid-sparing' effect, but there is evidence that the toxicity of methotrexate may also be increased and there is a risk of infection
Co-trimoxazole or trimethoprim	Concurrent use should be avoided

Topical fluorouracil	Avoid concurrent use (toxic skin reaction)
Leflunomide	Greater caution required (additive liver toxicity/hematology toxicity)
Oral neomycin	Monitor – as reduced absorption of methotrexate possible
Nitrous oxide	Antifolate effect of methotrexate increased by nitrous oxide – avoid concomitant use
Omeprazole	Possible increase in methotrexate toxicity (but information from case reports contradictory)
Penicillin's	There is evidence that some penicillin's can reduce the clearance of methotrexate, but acute methotrexate toxicity caused by this interaction has only been seen in a relatively small number of patients. Close monitoring is recommended.
Probenecid	Markedly increases serum methotrexate levels. Dosage reductions are needed to avoid toxicity.
Retinoids or ciclosporin	Greater caution should be taken when administering retinoids (acitretin) or ciclosporin concurrently with methotrexate
Salicylates and NSAIDs	Use with caution and monitor methotrexate dosage. Patients should be advised to avoid self-medication with over the counter aspirin or ibuprofen. (Avoid concomitant use with azapropazone)
Tetracycline / Doxycycline	Increased risk of toxicity when administered with methotrexate – careful monitoring required
Warfarin	Warfarin - monitor INR carefully
Unpasteurized milk, soft cheese etc	Be cautious of consuming foods which may have increased bacteria risk.

References:

Methotrexate (Hospira Brand) Summary of product characteristics, available at – (https://www.medicines.org.uk/emc/product/6789/smpc) Last updated 10/2017

The British National Formulary, Methotrexate, Available at – (https://bnf.nice.org.uk/drug/methotrexate.html)

METHOTREXATE FOR USE IN RHEUMATOLOGY (ADULT AND PAEDIATRIC), DERMATOLOGY, NEUROLOGY, GASTROENTEROLOGY, OPHTHALMOLOGY AND RESPIRATORY MEDICINE Shared care protocol – Oxford university hospitals – available at: https://www.ouh.nhs.uk/oxparc/professionals/documents/methotrexate-scp-july-2015.pdf

East and North Hertfordshire NHS Trust - Trust Guideline for Use of Oral Methotrexate, Shared Care Guideline for Adults – available at: http://www.enherts-tr.nhs.uk/files/2010/05/Methotrexate-Shared-Care.pdf

Inflammatory Arthritis: A Newly Recognized Adverse Event of Immune Checkpoint Blockade – The Oncologist – Available at: http://theoncologist.alphamedpress.org/content/22/6/627.full.pdf+html

Ocular myositis: diagnostic assessment, differential diagnoses, and therapy of a rare muscle disease – five new cases and review – Available at: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2699981/

Current and Future Role of Methotrexate in the Therapeutic Armamentarium for Rheumatoid Arthritis - Use of MTX in the Elderly – Medscape – Available at: https://www.medscape.com/viewarticle/761828_11