Managing Side Effects of Methotrexate

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Outline

COMMON	SERIOUS	RARE	PRACTICAL POINTS
Nausea/GI Lethargy/headache Transaminitis Stomatitis Neutropenia Alopecia Macrocytosis Lymphopenia	Pneumonitis Pancytopenia Interactions with other medications	Cancer risk	Pregnancy and fertility Vaccines Infection risk Alcohol

Methotrexate

- Dihydrofolic acid reductase inhibitor
- Weekly dosing only, takes at least 8 weeks to clinical benefit
- Blocking folic acid reduction prevents effective mitosis in rapidly dividing cells – leucocytes, hair follicles, mucosal cells
- Folic acid supplementation probably does not reduce efficacy of MTX, and does reduce risk of GI side effects, transaminitis, cessation, maybe stomatitis

Gastro intestinal Side Effects

- Nausea, Vomiting, less commonly diarrhoea
- Generally for up to 72 hours post dose
- Common upon commencement - often abate
- Manage by
  - Nocte dosing of MTX
  - Increase folic acid dose or frequency – up to 5mg 6 days per week
  - Change to Folinic acid 7.5mg or less 8-12 hours post MTX (leucovorin)

Lethargy/Headache

- Often in the 72 hours post dose not all week
- Can limit its use
- Folic acid and folinic acid not always helpful but worth a try
- Reduce dose by 5mg week first
- Discuss cessation with Rheum if severe and not responding to FA changes

MTX and Liver

- Incidence of transaminitis is about 10%
- Incidence of hepatotoxicity is less than this
- Routine liver biopsy after cumulative dose calculation not standard anymore
- Bloods are done monthly for 3-6 months and 3 monthly thereafter
- AST elevations are predictive of histological damage

MTX and Liver (cont)

- Consider other causes too – antibiotics, infection, alcohol
- REDUCE DOSE OR STOP
- If elevations are mild but persistent, reduce dose of MTX
- If severe/double (even if another cause likely), withold MTX 2 weeks and restart once bloods have normalised at lower dose with weekly testing
- Stop altogether if persist elevations

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MTX and Liver

- Combination MTX and Leflunomide is more common than either medication alone to raise LFT
- Therefore test 4-6 weekly on this combo
- Role of elastography unclear in routine monitoring
- Folic acid supplementation reduces chance of transaminitis

Stomatitis

- Oral mucositis – can be burning, mouth pain or frank ulceration
- Trials of folic acid mixed results for risk reduction
- Nonetheless if problematic
  - Increase FA dose or frequency to max 5mg 6 days weekly
  - Or change to folinic acid (leucovorin) 7.5mg 8-12 hours post dose

Neutropenia

- Dose dependent
- Folic acid unhelpful
- Stop if severe <1.0 until normal then rechallenge
- Consider observe if >1.0
- Consider other factors eg – disease itself (Felty’s, SLE), primary haematologic cause, ethnic, other medications

Alopecia

- People will notice increased shedding of hair then reduction of volume
- Consider other causes – telogen effluvium, SLE, hormonal (esp if male pattern)
- No evidence but try increasing FA dose or frequency or change to folinic acid
- Recovery indicated by slowing of shedding, regrowth can take time
- More common with Leflunomide

Macrocytosis

- Stable mild increases are a predicted effect of MTX therapy
- However increases with no dose change should prompt Ix for
  - B12 deficiency
  - Alcohol
  - Hypothyroidism
  - Hemolysis
  - Other drugs
  - Bone marrow disease (eg MDS)

Lymphopenia

- Mild lymphopenia a predicted albeit not always seen effect of treatment
- Consider lymphocyte subsets if levels below 0.8
- If CD4 count below 250, consider dose reduction or PJP prophylaxis (very uncommon on MTX alone)
- Sudden reduction with no change dose – consider other causes

MTX and Lung

- Hypersensitivity pneumonitis – acute fever, SOB cough rapid progression (days)
- Organising Pneumonia – subacute symptoms over weeks
- Pulmonary fibrosis
- Risk higher in
  - Age over 60
  - Diabetes
  - Serositis
  - Hypoalbuminemia
  - Other DMARDs

MTX and Lung

- Uncommon but seen in first 12 months
- No test diagnositic
  - Eosinophilia
  - Parenchymal markings or patchy consolidation on CXR, ground glass change on HRCT (or fibrosis)
  - Cultures negative including BAL
  - Eosinophils and granuloma on biopsy
  - Restrictive RFT reduction
  - Improvement with cessation

MTX and Lung

- Very broad differential
  - Infection includes opportunistic

- Managed with supportive care and glucocorticoids
- No role for folic acid or folinic acid

Pancytopenia

- High risk in
  - Elderly patients
  - Renal failure
  - Accidental daily instead of weekly dosing
  - Co administration of Trimethoprim-sulfamethoxazole or Probenecid

  - Managed with supportive care, removal causative factors, Leucovorin rescue (IV folinic acid 15mg QID)

Drug Interactions

- Avoid folate depleting drugs – trimethoprim-sulfamethoxazole, probenecid

- NSAIDs are safe to use with low dose (RA dose MTX) – previous concerns about impaired renal excretion of MTX and risk of cytopenia
- Leflumonide – LFT
- Azathioprine – potent T cell inhibition

Cancer Risk

- Lymphoma and Leukemia risk is double population norms for persons with RA, it is unclear if MTX independently increases risk

- Solid organ cancer risk not increased
- Previous cancer not a contraindication to use
- Probable increase in non melanoma skin cancer

Pregnancy and Fertility

- MTX no effect on female fertility
- BUT highly teratogenic
- Cease for 12 weeks prior to attempts at pregnancy (ie continue contraception for 12 weeks after stopping MTX)
- In males – possibility azoospermia or oligospermia, studies favour safety (no risk poor outcomes) but general practice is to cease for 12 weeks prior to attempts at pregnancy

Vaccines

- Safe to have influenza and Pneumococcal vax
- Response to vaccines can be assessed – Immunologist (IVIg or specific immunoglobulins)
- No live vaccines on MTX
- Stop for 12 weeks beforehand
  - Yellow fever
  - MMR
  - Shingles
  - Chickenpox
  - Oral polio
  - Rotavirus

Infection Risk

- Overestimated
- MTX alone not associated with increase risk of infections
- Shingles is the exception
- PJP – rare case reports alone
- We don’t stop prior to routine surgery
- Consider cessation for a few weeks if treating for severe or prolonged infection
- IgG levels should be measured if recurrent pulmonary infections

Alcohol

- Impossible to estimate liver response to both MTX and alcohol
- Often unfeasible to suggest complete abstinence and compliance likely to be poor
- 2-3 drinks per week reasonable
- Regular LFT testing paramount and will be best guide

- http://www.abc.net.au/radionational/programs/healthreport/re-embracing-methotrexate/8023350

- Dr Norman Swan interesting podcast about Methotrexate as a Nocebo.

Thanks