UNC INFLAMMATORY BOWEL DISEASE DRUG PROTOCOL

METHOTREXATE

Methotrexate is immunosuppressant that also exhibits anti-inflammatory activity. Methotrexate is commonly used for the treatment of certain cancers including but not limited to leukemia, Hodgkin’s disease and head and neck cancers. In these illnesses, methotrexate is used in very large doses so that it interferes with the reproduction of the cancer cells. Methotrexate is used in smaller doses for the treatment of rheumatoid arthritis, Crohn’s disease and psoriasis. Clinical trials have demonstrated efficacy of Methotrexate in induction and maintenance of remission in Crohn’s disease.

TREATMENT PROTOCOL:

Current indications for methotrexate at UNC:
1. Induction of remission in patients with steroid-dependent Crohn's disease
2. Maintenance of remission in mild to moderate Crohn's disease patients
3. Use in combination therapy with biologics to reduce immunogenicity
4. Patients with poor tolerance to thiopurines and require immunomodulator therapy
5. Patients with active Crohn's disease and concomitant active inflammatory arthritis.
6. Use in ulcerative colitis still experimental, but efficacy suggested by case series and one placebo-controlled trial

Dosage and route of administration:
- Methotrexate is available in 25 mg/ml vials or in 2.5 mg tablets.
- Parenteral formulation:
  - Dose for induction of remission is 25 mg per week (1ml) x 16 weeks. For maintenance a dose of 25 mg/week is also suggested, some patient may do well with reduced dose of 15 mg weekly but not all.
  - For parenteral dosing the patient is taught self-injection techniques in the clinic. Subcutaneous rather than IM injections are used with less morbidity seen.
  - Preferable form for patients with small bowel Crohn’s disease as small bowel inflammation is associated with variable bioavailability of oral methotrexate
- Oral dosing:
  - May be used for colonic disease or in the settings of combination therapy.
  - Initial dosing similar to parenteral dosing (25 mg weekly) is suggested. However, an oral dose higher that 15 mg may be associated with reduced bioavailability and generally, if oral MTX at dose ≥ 15 mg is
ineffective parenteral application is recommended. Alternatively, splitting the total dose in 2 oral applications, taken 8 hours apart, has been shown to improve the bioavailability of oral MTX.

- Current dose for combination therapy with biologics $\geq 15 \text{ mg} \leq 25 \text{ mg}$.
  - Folate: patients should receive 1 mg/day or a single 5 mg/week dose of folate while they are receiving methotrexate due to interference with folate metabolism. Low dose folate does not interfere with the efficacy of the methotrexate.

**Time for response:** 6 weeks to 3 months

**Contraindications:**

- **Relative:** creatinine clearance of less than 50 ml/minute, Hx of recurrent significant dehydration, active liver disease, alcoholism, fatty liver disease (obesity, diabetes) and active pulmonary disease, albumin $<2.5 \text{ mg/dl}$ (associated with increased risk of toxicity).
- **Absolute:** pregnancy or contemplating pregnancy and breast-feeding. Patients should be advised to continue contraception for at least 3 months after stopping methotrexate.

**Laboratory monitoring:**

<table>
<thead>
<tr>
<th>Pre-treatment</th>
<th>Subsequent monitoring</th>
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<tbody>
<tr>
<td>1. CBC with differential</td>
<td>CBC, LFTs, Albumin, BUN/Creatinine every 2 weeks until dose and labs are stable. Frequency can be then spaced to every 8-12 weeks</td>
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<tr>
<td>2. BUN/ Creatinine</td>
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<tr>
<td>3. AST, ALT, Alkaline Phosphatase, GGT, T. Bilirubin, Albumin</td>
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<td>4. Urinalysis</td>
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<td>5. Hepatitis A, B and C serologies</td>
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<td>6. Assess HIV risk and appropriate testing as indicated.</td>
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<td>7. Chest X-ray (if abnormal, HRCT and PFT can be performed)</td>
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**Special considerations:**

- **Nausea:** about 25% of treated patients will experience nausea. This often can be well-controlled and/or avoided with concomitant zofran (ondansetron) 8mg tablets given 1 to 2 hours before and 12 to 24 hours after the MTX dose.
Liver toxicity: Methotrexate should be stopped if there is a confirmed increase in ALT/AST greater than three times the ULN, but may be reinstituted at a lower dose following normalization. In patients with elevated liver enzymes, would suggest repeating levels one week after the last dose. If levels normalized, then may resume methotrexate at a lower dose. However, if elevation persistent, withhold methotrexate for one to two weeks and repeat enzymes. Enzyme levels should return to normal within one to two weeks. Persistent elevation for two to three months warrants further evaluation with liver biopsy or non-invasive assessment for fibrosis. Liver biopsy is not routinely indicated based on the cumulative dose.

Bone marrow suppression: If leukocytes count < 3,500/mm³ (continuing beyond one week) and/or platelet count < 100,000/mm³, hold therapy and restart therapy after three weeks at 50 to 75 percent of original dose.

Anemia with MCV > 100 μm³/cell (100 fL), obtain vitamin b12, folate, and TSH levels

Renal impairment: Do not use in patients with an estimated CrCl < 50 mL per minute.

Immunizations: Patients receiving methotrexate must not receive immunization with live vaccines. General vaccination recommendations for IBD patients apply.

References:


