

BCCA Protocol Summary for Treatment of Meningeal Disease (Miscellaneous Tumour Origins) using High Dose Methotrexate with Leucovorin Rescue

Protocol Code

UMOHDMTX

Tumour Group

Miscellaneous Origins

Contact Physician

Dr. Meg Knowling

ELIGIBILITY:

- Meningeal disease (miscellaneous tumour origins)
- Not progressed on previous high dose Methotrexate
- Life expectancy **greater than** 12 wks
- A BCCA “Individual Use of Benefit Drug List Medication for an Undesignated Indication” form must be approved

EXCLUSIONS:

1. Serum creatinine above 150 **micromol/L** or estimated creatinine clearance below 60 mL/min

$$\text{Estimated creatinine clearance:} = \frac{N (140 - \text{age}) \text{ wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

$$N = \begin{matrix} 1.23 \text{ male} \\ 1.04 \text{ female} \end{matrix}$$

2. Pleural effusion, ascites, full extremity edema.

3. Hemoglobin **less than** 90 g/L; neutrophils **less than** $1.5 \times 10^9/L$; platelets **less than** $75 \times 10^9/L$

4. AST, alkaline phosphatase or total bilirubin **greater than** twice upper limit of normal

TESTS:

- Baseline and pretreatment: CBC & diff, platelets, serum creatinine, lytes, AST, bilirubin, alkaline phosphatase, urine pH, chest radiograph.
- Chest radiograph at least monthly to rule out effusion
- Immediately pre-methotrexate and q6h: urine pH
- Daily qam during treatment: serum creatinine, lytes, methotrexate levels (until **less than** 0.05 **micromol/L**; note date and time of withdrawal on the specimen)

PREMEDICATIONS:

Ondansetron 8 mg PO or IV before Methotrexate
Prochlorperazine 10 mg PO after Methotrexate infusion completed and then 10 mg PO q4h PRN

TREATMENT:

Patients must have creatinine clearance **greater than** 60 mL/min and vigorous IV hydration and urine alkalinization to maintain urine pH above 7.

Alkalinizing Regimen and Prehydration:
▪ IV 2/3 : 1/3 + 100 mEq sodium bicarbonate/L + 20 mEq KCL/L at 125 ml/h x 4 hours pre-methotrexate
▪ Oral sodium bicarbonate 3000 mg PO q4h until methotrexate level less than 0.05 micromol/L (start concurrent with IV bicarbonate prehydration)
▪ Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than or equal to 7 before starting methotrexate.

DRUG	DOSE	BCCA ADMINISTRATION GUIDELINES
Methotrexate	1-12 g/m ² (Day 1)	IV in 1L NS over 4 hours
Leucovorin	25 mg q6h (start Day 2)	Starting exactly 24 hours after start of Methotrexate infusion; IV for 4 doses then PO until Methotrexate level less than 0.05 micromol/L*
Posthydration		IV 2/3 : 1/3 + 100 mEq sodium bicarbonate/L + 20 mEq KCL/L at 125 mL/h for 48 hours after Methotrexate

If well tolerated, may be given q 1-4 weekly.

*Methotrexate must be given in a hospital where rapid reporting of methotrexate levels is available. Leucovorin dose modifications commence on day 3 based on that morning's methotrexate level (ie, level drawn 36-48 hours following the start of the methotrexate infusion). Methotrexate levels are repeated qam and the leucovorin dose is adjusted until methotrexate level **less than** 0.05 micromol/L as follows:

Methotrexate Level (micromol/L=10⁻⁶ mol/L)	Leucovorin Dose
0.05	none
0.05 – 0.9	25 mg q6h
1.0 – 8.0	100 mg/m ² q6h
greater than 8.0	1000 mg/m ² q6h

DOSE MODIFICATIONS:

1. Hematological

ANC x 10 ⁹ /L		Platelets x 10 ⁹ /L	Dose
greater than or equal to 1.5	and	greater than or equal to 75	100%
less than 1.5	or	less than 75	delay 1 week and reassess

2. Renal Dysfunction:

- If CrCl **less than** 60 mL/min, reversible causes of renal dysfunction should be treated and the patient reassessed for suitability for this treatment once renal function improves.
- If serum creatinine obtained 20-24 hours after starting methotrexate is increased **greater than** 50% above baseline, increase leucovorin to 100 mg/m² q6h.

3. Mucositis **greater than or equal to** Grade 3 (painful erythema, edema or ulcers and cannot eat), reduce methotrexate to 80% or prolong routine rescue for 2 more days (unless abnormal methotrexate levels).

PRECAUTIONS:

1. **Third space fluids:** Patients with clinically or radiologically detectable third space fluid (e.g. pleural effusion, ascites, full extremity pitting edema) should NOT be given high dose methotrexate.
2. **Renal elimination:** Patients with elevated serum creatinine or calculated creatinine clearance below 60 mL/min should NOT receive high dose methotrexate. Avoid concomitant use of drugs that may inhibit renal elimination of methotrexate such as non-steroidal anti-inflammatories (NSAIDs), salicylates and sulfa drugs.

Call Dr. Meg Knowling or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

Date activated: 23 July 1999

Date last revised: 01 May 2009 (unsafe abbreviations and symbols replaced)

REFERENCES:

Bleyer WA. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. Cancer Treat Rev 1977;4:87-101.