

BC Cancer Protocol Summary for Treatment of Meningeal Disease using High-Dose Methotrexate with Leucovorin Rescue

Protocol Code

BRAVHDMTX

Tumour Group

Breast Tumour Group

Contact Physician

Dr. Angela Chan

ELIGIBILITY:

- Meningeal disease in breast and miscellaneous tumour origins
- Not progressed on previous high dose methotrexate
- Life expectancy greater than 12 weeks

EXCLUSIONS:

1. Serum creatinine above 150 micromol/L or estimated creatinine clearance below 60 mL/min as calculated by Cockcroft/Gault formula –see page 3
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: CBC & diff, platelets, serum creatinine, sodium, potassium, ALT, bilirubin, alkaline phosphatase, urine pH, chest radiograph.
- Chest radiograph at least monthly to rule out effusion
- Immediately pre-methotrexate and q6h: urine pH
- Daily in morning during treatment: serum creatinine, sodium, potassium, methotrexate levels (until less than 0.1 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 alkalization to maintain urine pH above 7.

| START ALKALINIZING REGIMEN 4 TO 12 HOURS PRIOR TO METHOTREXATE: |
|--|
| <ul style="list-style-type: none">Discontinue all other IV hydration before starting alkalinizing regimen. |
| <ul style="list-style-type: none">IV D5W with potassium chloride 20 mEq/L and sodium bicarbonate 150 mEq/L at 125 mL/h for at least 4 hours prior to methotrexate until urine pH is greater than 7. Hydration may be temporarily held during methotrexate infusion (per physician/nursing discretion). Continue hydration post-methotrexate infusion until methotrexate level is less than 0.1 micromol/L. |
| <ul style="list-style-type: none">Check urine pH before starting methotrexate. If pH less than 7, continue alkalinizing regimen until urine pH greater than 7 before starting methotrexate. |

| DRUG | DOSE | BC Cancer Administration Guidelines |
|--------------|---|--|
| methotrexate | 1 to 12 grams/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 0.1 micromol/L * |

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

NOTE: One staff Physician signature is required. Orders written by **other providers** MUST be co-signed.

*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 (i.e. level drawn 36-48 hours following the start of the methotrexate infusion). Methotrexate levels are repeated q am and the leucovorin dose is adjusted until methotrexate level less than 0.1 micromol/L as follows:

| Methotrexate Level (micromol/L= 10^{-6} mol/L) | Leucovorin Dose |
|--|----------------------------|
| 0.1 | none |
| 0.1 to 0.9 | 25 mg q6h |
| 1.0 to 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.

• **Cockcroft/Gault formula:**

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

N = 1.23 male
1.04 female

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.
3. **Possible interactions with proton pump inhibitors (e.g. pantoprazole, omeprazole, lansoprazole)** have been reported, resulting in elevated methotrexate levels and increased risk of methotrexate toxicity. Consider discontinuing proton pump inhibitors 1 day prior to methotrexate administration. If their use is required, closely monitor methotrexate levels and monitor for signs of methotrexate toxicity.

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

REFERENCES:

1. Bleyer WA. Methotrexate: clinical pharmacology, current status and therapeutic guidelines. *Cancer Treat Rev* 1977;4:87-101.
2. Ranchon F, Vantard N, Gouraud A, et al. Suspicion of drug-drug interaction between high-dose methotrexate and proton pump inhibitors: a case report – should the practice be changed? *Chemotherapy* 2011;57(3):225-9.