

BCCA Protocol Summary for Treatment of Osteosarcoma Using High Dose Methotrexate with Leucovorin Rescue

Protocol Code	SAHDMTX
Tumour Group	Sarcoma
Contact Physician	Dr. Meg Knowling

ELIGIBILITY:

- Patients who have metastatic or locally recurrent disease AND who have previously received doxorubicin and cisplatin (SAAJAP or SAAVAP) and/or ifosfamide and etoposide (SAIME)
- Life expectancy **greater than** 3 months

EXCLUSIONS:

- Progression on previous high dose methotrexate
- Serum creatinine **greater than** 150 micromol/L or estimated creatinine clearance **less than** 60 mL/min:

$$\text{Creatinine clearance} = \frac{N * (140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine}}$$

* For males N= 1.23; For females N=1.04

- Pleural effusion, ascites or full extremity edema
- Hemoglobin **less than** 90 g/L; neutrophils **less than** $1.5 \times 10^9/L$; platelets **less than** $75 \times 10^9/L$
- AST, alk phos or total bilirubin **greater than** 2 x ULN

TESTS:

- Baseline and before each treatment: CBC & diff, platelets, creatinine, lytes, bilirubin, AST, alk phos, GGT, LDH, urine pH, chest x-ray
- Chest x ray at least monthly to rule out effusion
- Urine pH immediately prior to treatment and every 6 hours during treatment
- Daily creatinine and lytes
- Daily methotrexate level in morning starting on day 2 until MTX **less than** 0.05 micromol/L (note date and time of withdrawal as well as start time of infusion on specimen)

PREMEDICATIONS:

- Ondansetron 8 mg PO/IV immediately prior to methotrexate
- Prochlorperazine 10 mg PO once after methotrexate infusion completed and 10 mg PO q4h prn

ALKALINIZING REGIMEN & HYDRATION:

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

Pre-methotrexate:	<ul style="list-style-type: none">IV 2/3 D5W:1/3 NS + 100 mEq sodium bicarbonate/L + 20 mEq KCl/L at 125 mL/hr x 4 hoursOral 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
Post-methotrexate:	<ul style="list-style-type: none">IV 2/3 D5W:1/3 NS + 100 mEq sodium bicarbonate/L + 20 mEq KCl/L at 125 mL/hr for 48 hours after methotrexate

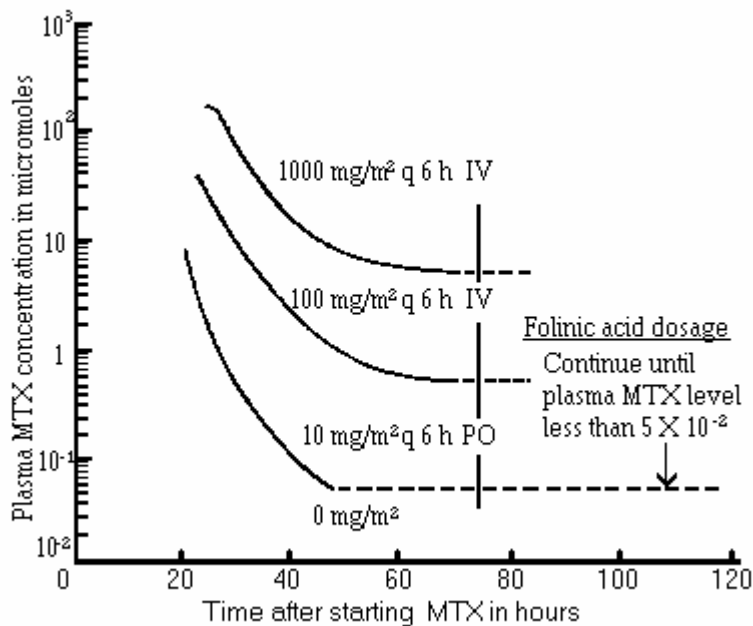
TREATMENT:

Drug	Dose	BCCA Administration Guideline
Methotrexate	8 000 – 12 000 mg/m ² on day 1	IV in 1 L NS over 4 hours
Leucovorin	25 mg q6h (start day 2)	Starting exactly 24 hours after start of methotrexate infusion; IV x 4 doses, then PO until methotrexate level less than 0.05 micromol/L*

Repeat every 1 to 4 weeks

NOTE: Two physicians' signatures are required on the medication orders (one must be a medical oncologist).

* Methotrexate must be given in the hospital setting where rapid reporting of methotrexate levels is available. Plasma methotrexate levels are performed routinely each morning after starting the methotrexate infusion. At 24 hours, leucovorin rescue begins according to the protocol at an initial dose of 25 mg q6h. The plasma methotrexate concentrations done on day 2 and day 3 are used to plot the initial slope of the curve on the Bleyer diagram below, but only the methotrexate concentrations done on day 3 should be used to increase the dose of leucovorin, if necessary. Leucovorin is continued until the plasma methotrexate is, or is projected to be, less than 0.05×10^{-6} molar (0.05 micromol/L).



Reference: Bleyer WA. The clinical pharmacology of methotrexate – new applications of an old drug. Cancer 1978; 41:36-51.

DOSE MODIFICATIONS:

1. Hematological

Sample Table:

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	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 creatinine clearance on treatment day is **less than** 60 mL/min, treat reversible causes of renal dysfunction and reassess suitability of this protocol for patient once renal function improves
- If serum creatinine obtained 20-24 hours after starting methotrexate has increased **greater than** 50% above baseline, increase leucovorin to 100 mg/m² q6h

3. **Mucositis:** Grade 3 or 4 (painful erythema, edema, ulcers and cannot eat), reduce methotrexate to 80% or prolong routine rescue by 2 more days (unless patient has abnormal methotrexate levels)

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BCCA Febrile Neutropenia Guidelines.
2. **Third space fluids:** Patients with clinically or radiologically detectable third space fluids (e.g. pleural effusion, ascites, full extremity pitting edema) should NOT be given high dose methotrexate.
3. **Renal elimination:** Patients with elevated serum creatinine levels or calculated creatinine clearance **less than** 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-inflammatory drugs (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: **N/A (as OSHDMTX)**

Date revised: 1 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.