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

**Protocol Code** SAHDMTX

**Tumour Group** Sarcoma

**Contact Physician** Dr. Christine Simmons

**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:
  \[
  \text{Creatinine clearance} = \frac{N \times (140 - \text{Age}) \times \text{Weight (kg)}}{\text{Serum creatinine}}
  \]
  * 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 x 10^9/L; platelets less than 75 x 10^9/L
- ALT, alk phos or total bilirubin greater than 2 x ULN

**TESTS:**
- Baseline and before each treatment: CBC & diff, platelets, creatinine, sodium, potassium, bilirubin, ALT, 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 0.1 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: | ▪ IV 2/3 D5W:1/3 NS + sodium bicarbonate 100 mEq /L + potassium chloride 20 mEq /L at 125 mL/h x 4 hours |
| Post-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 |

Post-methotrexate: ▪ IV 2/3 D5W:1/3 NS + sodium bicarbonate 100 mEq /L + potassium chloride 20 mEq /L at 125 mL/h for 48 hours after methotrexate

TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
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<tbody>
<tr>
<td>methotrexate</td>
<td>8 to 12 grams/m² on day 1</td>
<td>IV in 1000 mL NS over 4 hours</td>
</tr>
<tr>
<td>leucovorin</td>
<td>25 mg q6h (start day 2)</td>
<td>Starting exactly 24 hours after start of methotrexate infusion; IV x 4 doses, then PO until methotrexate level LESS THAN 0.1 micromol/L*</td>
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Repeat every 1 to 4 weeks

NOTE: One staff Physician signature is required. Orders written by residents and fellows MUST be co-signed.

* 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 0.1 X 10⁻⁶ molar (0.1 micromol/L).

Note: New laboratory method has a higher limit of detection and inaccuracies have been reported with methotrexate levels below 0.1 micromol/L.

DOSE MODIFICATIONS:

1. Hematological

<table>
<thead>
<tr>
<th>ANC (x10⁹/L)</th>
<th>Platelets (x10⁹/L)</th>
<th>Dose</th>
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<tbody>
<tr>
<td>greater than or equal to 1.5 and greater than or equal to 75</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>less than 1.5 or less than 75</td>
<td>Delay 1 week and reassess</td>
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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 BC Cancer 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.
4. **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. Christine Simmons or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

**References:**