BC Cancer Protocol Summary for Neoadjuvant and Adjuvant Therapy for Osteosarcoma using High-Dose Methotrexate, DOXOrubicin, and CISplatin

Protocol Code	*SANAHDMAP*
Tumour Group	*Sarcoma*
Contact Physician	*Dr. Alannah Smrke*

ELIGIBILITY:

Patients must have:
- Biopsy proven osteosarcoma,
- Age under 40 years, and
- Fit to undergo aggressive curative intent treatment

Patients should have:
- Normal renal, cardiac and hepatic function

EXCLUSIONS:

Patients must not have:
- Calculated creatinine clearance less than 60 mL/min
- Total bilirubin greater than 85 micromol/L
- Large third space fluid accumulations (significant ascites, large pleural effusion or other large lobulated fluid accumulations)

TESTS:

- Baseline: CBC & Diff, sodium, potassium, creatinine, calcium, magnesium, albumin, total bilirubin, alkaline phosphatase, ALT, LDH, GGT, urine pH, chest x-ray
- Baseline, if clinically indicated: MUGA scan or echocardiogram, audiogram/hearing test
- Prior to Day 1 of each treatment: CBC & Diff, sodium, potassium, creatinine, calcium, magnesium, albumin, total bilirubin, alkaline phosphatase, ALT, LDH, GGT
- Methotrexate orders (in addition to tests above):
  - Chest x-ray: Prior to each methotrexate dose
  - Urine pH: Immediately pre-methotrexate and q6H until methotrexate level less than 0.1 micromol/L (See Alkalinizing regimen, below)
  - Creatinine, sodium, and potassium: Every morning during methotrexate treatment, and continued until methotrexate level less than 0.1 micromol/L (starting morning after each methotrexate dose)
  - Methotrexate levels: At hour 48 from start of each methotrexate infusion, or morning of Day 3 (methotrexate given on Day 1) then once daily every morning until methotrexate levels less than 0.1 micromol/L
    - Note date and time of withdrawal as well as start time of infusion on specimen
    - MD to be notified of all results immediately

- Daily ALT, total bilirubin, alkaline phosphatase, LDH, and GGT: Optional if clinically indicated starting day after each methotrexate dose, and continued until methotrexate level less than 0.1 micromol/L

** IMPORTANT NOTE: use the ***same*** renal function measure throughout the treatment course, i.e., if estimated GFR was used initially, subsequent dosing should be based on GFR and ***not*** creatinine clearance

PREMEDICATIONS:

Cycles 1 to 4, Week 1

- For DOXOrubicin and CISplatin:
  - aprepitant 125 mg PO 30 minutes prior to treatment on Day 1, then 80 mg PO once daily on Days 2 and 3, and
  - ondansetron 8 mg PO/IV 30 minutes prior to treatment on Days 1 and 2, in the evening on Days 1 and 2, and BID on Days 3 and 4,
  - dexamethasone 8 mg PO/IV 30 minutes prior to treatment on Days 1 and 2, in the evening on Days 1 and 2, and BID on Days 3 and 4, and
  - olanzapine 2.5 to 5 mg PO 30 minutes prior to treatment on Days 1 and 2, once daily in the evening on Days 3 to 5.
  - at discharge: continue aprepitant, ondansetron, dexamethasone and olanzapine for any remaining days listed above not given as inpatient.

Cycles 1 to 4, Weeks 4 and 5

- For methotrexate:
  - ondansetron 8 mg PO/IV 30 minutes prior to treatment on Day 1
  - prochlorperazine 10 mg PO after methotrexate infusion completed

Cycles 5 and 6, Week 1:

- For DOXOrubicin:
  - ondansetron 8 mg PO/IV 30 minutes prior to treatment on Days 1 and 2, in the evening on Days 1 and 2, and BID on Days 3 and 4
  - dexamethasone 8 mg PO/IV 30 minutes prior to treatment on Days 1 and 2, in the evening on Days 1 and 2, and BID on Days 3 and 4

Cycles 5 and 6, Weeks 3 and 4:

- For methotrexate:
  - ondansetron 8 mg PO/IV 30 minutes prior to treatment on Day 1
  - prochlorperazine 10 mg PO after methotrexate infusion completed

PRN Medications and Supportive Care:
Cycles 1 to 4, Week 1:

- For DOXOrubicin and CISplatin:
  - LORazepam 1 mg SL q4h PRN nausea, sleep or restlessness
  - prochlorperazine 10 mg PO q6h PRN nausea
  - dimenhyDRINATE 50 mg PO/IV q4h PRN nausea
  - nabilone 1 to 2 mg PO q8h PRN nausea
  - filgrastim is mandatory for primary prophylaxis of neutropenia. Submit a special authority request to Pharmacare for filgrastim coverage. See Treatment, below.

Cycles 1 to 4, Weeks 4 and 5

- For methotrexate:
  - prochlorperazine 10 mg PO q6h prn nausea

Cycles 5 and 6, Week 1:

- For DOXOrubicin:
  - prochlorperazine 10 mg PO q6h prn nausea
  - filgrastim is mandatory for primary prophylaxis of neutropenia. Submit a special authority request to Pharmacare for filgrastim coverage. See Treatment, below.

Cycles 5 and 6, Weeks 3 and 4:

- For methotrexate:
  - prochlorperazine 10 mg PO q6h prn nausea

Treatment Schema:

Treatment/Week	Acronym
DOXOrubicin (A) and CISplatin (P)	AP
methotrexate (M) and leucovorin	M
DOXOrubicin monotherapy (A)	A

Cycle	1					2						3					4				
Week	1	2	3	4	5	1	2	3	4	5		1	2	3	4	5	1	2	3	4	5
Day	1, 2			1	1	1,2			1	1	Surgery*	1,2			1	1	1,2			1	1
Drug	A P			M	M	A P			M	M		A P			M	M	A P			M	M

* There is a treatment break between Cycles 2 and 3. Liaise with surgeon when to restart treatment. Treatment should be restarted once cleared by surgical team. Typically chemotherapy is restarted 2-3 weeks after surgery.

Cycle	5				6			
Week	1	2	3	4	1	2	3	4
Day	1, 2		1	1	1, 2		1	1
Drug	A		M	M	A		M	M

TREATMENT:

- Note: Treatment should be administered as an inpatient (exception: Cycle 5 and 6, Week 1 DOXOrubicin may be administered as outpatient)

Cycles 1, 2, 3, and 4

- Cycles 1 to 4 are five weeks in length

Cycles 1 to 4: Week 1

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	37.5 mg/m^2 on Days 1 and 2	IV push
CISplatin* †	50 mg/m^2 on Days 1 and 2	IV in 1000 mL NS with potassium chloride 10 mEq and 30 g mannitol over 2 hours
filgrastim	5 mcg/kg once daily for 5 days** starting on Day 3 300 mcg: up to 75 kg 480 mcg: 76 kg to 110 kg 600 mcg: greater than 110 kg	Subcutaneously
See Weeks 4 and 5 methotrexate below		

† See Hydration, below

* 60 mg/m^2 on Days 1 and 2 may be given in exceptional circumstances per provider discretion

**adjust duration based on repeat neutropenia and any treatment delays

† **HYDRATION:**

Pre-CISplatin:	D5W-1/2NS 1000 mL with potassium chloride 20 mEq and magnesium sulfate 2 g IV over 3 h. Prior to beginning **CISplatin**, urine output must be greater than or equal to 300 mL in 3 h. May repeat prehydration x 1 L to ensure urine output greater than 300 mL in 3 h. If urine output not adequate after 2 L, notify MD.
Post-CISplatin:	D5W-1/2NS with potassium chloride 20 mEq/L and magnesium sulfate 2 g/L at 200 mL/h for 12 h. Measure every 3 h input and output while on IV. If output less than 300 mL during a 3 h period, increase IV to 300 mL/h for 3 h. If urine output still less than 300 mL in a subsequent 3 h period, give **furosemide** 20 mg IV x 1. If output still not adequate, notify MD. May discontinue IV and discharge after post hydration if urine output adequate and patient not vomiting.

Cycles 1 to 4: Weeks 4 and 5

Drug	Dose	BC Cancer Administration Guideline
methotrexate** ¶ ‡	12 grams/m^2 on Day 1 (**Maximum dose: 20 grams**)	IV in 1000 mL NS over 4 hours
leucovorin***	25 mg q6h starting on Day 2	Starting exactly 24 hours after start of methotrexate infusion; IV for 4 doses then PO until methotrexate level IS LESS THAN 0.1 micromol/L

** Patients must have GFR (or CrCl) greater than 60 mL/min and vigorous IV hydration and urine alkalinization to maintain urine pH above 7

¶ Note: One staff physician signature is required. Methotrexate orders written by other providers MUST be cosigned.

‡ See Alkalinizing regimen, below

*** See Methotrexate levels, below

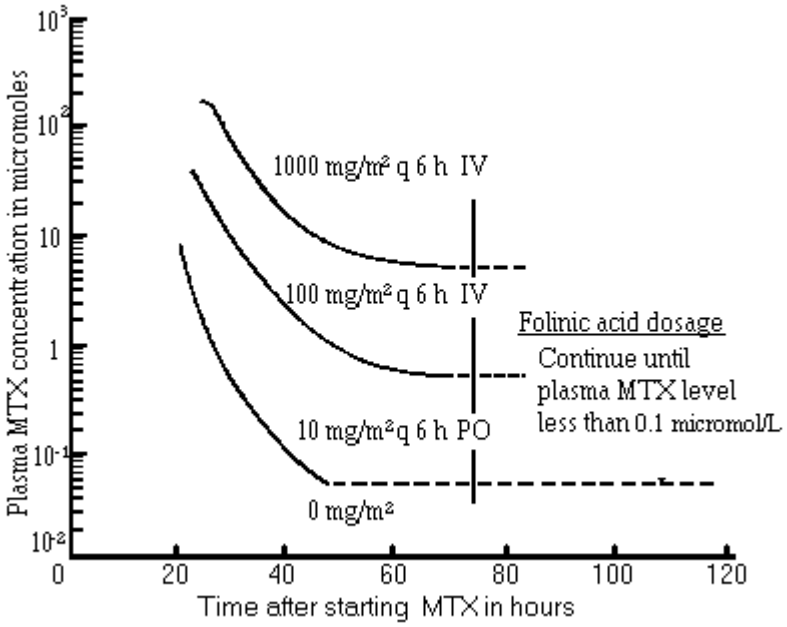
‡ **Alkalinizing regimen:**

- **START ALKALINIZING REGIMEN 4 TO 12 HOURS PRIOR TO METHOTREXATE:**

▪ Discontinue all other IV hydration before starting alkalinizing regimen.
▪ 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.
▪ 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.

*** **methotrexate levels:**

- methotrexate must be given in a hospital 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. A dose of leucovorin 25 mg q6h is used initially. The plasma methotrexate concentration that is done at hour 48 h from the start of the methotrexate infusion is used to plot the initial slope of the curve on the Bleyer diagram below and 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 (note: micromoles/L = 10^{-6} molar).



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

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

Cycles 5 and 6:

- Cycle 5 starts five weeks after Cycle 4
- Cycles 5 and 6 are four weeks in length

Cycles 5 to 6: Week 1

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	37.5 mg/m^2 on Days 1 and 2	IV push
filgrastim	5 mcg/kg daily for 5 days* starting on Day 3 300 mcg: up to 75 kg 480 mcg: 76 kg to 110 kg 600 mcg: greater than 110 kg	Subcutaneously

* adjust duration based on repeat neutropenia and any treatment delays

Cycles 5 to 6: Weeks 3 and 4

Drug	Dose	BC Cancer Administration Guideline
methotrexate** ¶ ‡	12 grams/m^2 on Day 1 (**Maximum dose: 20 grams**)	IV in 1000 mL NS over 4 hours
leucovorin***	25 mg q6h starting on Day 2	Starting exactly 24 hours after start of methotrexate infusion; IV for 4 doses then PO until methotrexate level IS LESS THAN 0.1 micromol/L

** Patients must have GFR (or CrCl) greater than 60 mL/min and vigorous IV hydration and urine alkalinization to maintain urine pH above 7

¶ Note: One staff physician signature is required. Methotrexate orders written by other providers MUST be cosigned.

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‡ **Alkalinizing regimen:**

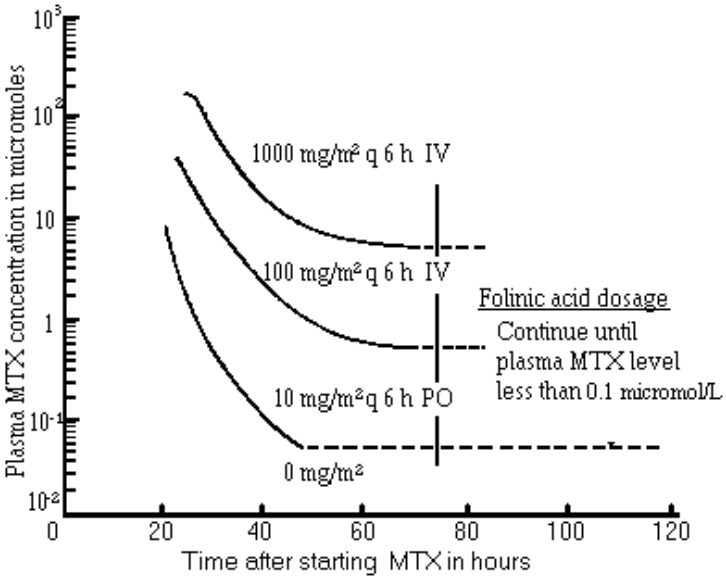
- **START ALKALINIZING REGIMEN 4 TO 12 HOURS PRIOR TO METHOTREXATE:**

▪ Discontinue all other IV hydration before starting alkalinizing regimen.
▪ 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.
▪ 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.

*** **methotrexate levels:**

- methotrexate must be given in a hospital 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. A dose of leucovorin 25 mg q6h is used initially. The plasma methotrexate concentration that is done at hour 48 h from the start of the methotrexate infusion is used to plot the initial slope of the curve on the Bleyer diagram below and 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 (note: micromoles/L = 10^{-6} molar).

Reference: Bleyer WA. The clinical pharmacology of methotrexate – new applications



of an old drug. Cancer 1978; 41:36-51.

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 (for DOXOrubicin, CISplatin, and methotrexate):

- For DOXOrubicin and CISplatin, or DOXOrubicin monotherapy:

ANC (x10^9/L)		**Platelets (x10^9/L)**	**DOXOrubicin dose**	**CISplatin dose** (if applicable)
Greater than or equal to 0.75	and	Greater than or equal to 75	100%	100%
Neutropenic fever with ANC less than 0.5	and	any	Delay until ANC 0.75, then 100%	Delay until ANC 0.75, then 75%
Less than 0.75	or	Less than 75	Delay 1 week	Delay 1 week

- For methotrexate:

ANC (x10^9/L)		**Platelets (x10^9/L)**	**methotrexate dose**	**leucovorin dose**
Greater than or equal to 0.25	and	Greater than or equal to 50	100%	100%
Less than 0.25	or	Less than 50	Delay 1 week*	Delay 1 week*

*avoid repeated delays that impact delivery of subsequent cycles of DOXOrubicin (A) and/or CISplatin (P)

2. Renal Dysfunction (for DOXOrubicin, CISplatin, and methotrexate):

- For CISplatin:

  Calculate creatinine clearance with each cycle using the following formula:

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

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

  - Dose reduction for CISplatin should be considered if creatinine clearance changes to less than **60 mL/min**
  - If serum creatinine done next day after hydration remains elevated, consider dose reduction for CISplatin:

Creatinine clearance (mL/min)	CISplatin dose	DOXOrubicin dose (Cycles 1 to 4)
Greater than or equal to 60	100%	100%
45 to less than 60	80%	100%
Less than 45	Delay 1 week. Consider additional IV fluids	Delay 1 week. Consider additional IV fluids

- For methotrexate:
  - Patients must have GFR (or creatinine clearance) greater than **60 mL/min** and vigorous IV hydration and urine alkalinization to maintain urine pH above 7.[1]

Creatinine clearance (mL/min)	methotrexate dose
Greater than or equal to 60	100%
Less than 60	Patients should NOT receive high dose methotrexate. Reversible causes of renal dysfunction should be treated and the patient reassessed for suitability for methotrexate treatment once renal function improves.

****IMPORTANT NOTE: Use the ***same*** renal function measure throughout the methotrexate treatment course, i.e., if estimated GFR was used initially, subsequent dosing should be based on GFR and ***not*** creatinine clearance

3. Hepatic dysfunction (for DOXOrubicin, CISplatin, and methotrexate):

- For DOXOrubicin and CISplatin, or DOXOrubicin monotherapy:

Total bilirubin (micromol/L)		ALT or AST	DOXOrubicin dose	CISplatin dose (if applicable)
Less than ULN	and	Less than ULN	100%	100%
-		2 to 3 x ULN	75%	
20 to 50	or	Greater than 3 x ULN	50%	
51 to 85		-	25%	
Greater than 85		-	Do not administer	

- For methotrexate:
  - At high doses, methotrexate can cause elevation of bilirubin and other liver enzymes. Even though these abnormalities are generally reversible, delaying treatment until liver enzymes significantly improve or return to near normal values before starting the next cycle is recommended. The table below may be used as a guide to dose reductions
  - Maximum doses are prorated, e.g., for 75% dose modification, maximum dose = 15 grams

Total bilirubin (micromol/L)		ALT or AST	methotrexate dose	leucovorin dose
2 to 49		-	100%	100%
50 to 85	or	3 x ULN	75% (Maximum dose: 15 grams)	100%
Greater than 85		-	Omit	Omit

4. **Mucositis (for DOXOrubicin and methotrexate):**
   - For DOXOrubicin:

Grade	Description	DOXOrubicin dose
3	Severe pain; interfering with oral intake	80%
4	Life threatening consequences; urgent intervention indicated	

   - For methotrexate:
     - Maximum doses are prorated, e.g., for 80% dose modification, maximum dose = 16 grams

Grade	Description	methotrexate dose
3	Severe pain; interfering with oral intake	• 80% (Maximum dose: 16 grams) or • Prolong routine rescue for 2 more days (unless abnormal methotrexate levels)
4	Life threatening consequences; urgent intervention indicated	

5. **Nausea & Vomiting** (DOXOrubicin and CISplatin)**:**
   - if Grade 4 despite optimal use of antiemetics

Grade	Description	DOXOrubicin and CISplatin doses
4	Life threatening consequences; urgent intervention indicated	• 80% or • Discontinue

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 GFR (or 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. **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycosides.
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 if required, closely monitor methotrexate levels and monitor for signs of methotrexate toxicity.

5. **Possible interaction with penicillins (e.g., amoxicillin, piperacillin, ticarcillin).** Penicillins compete with methotrexate for excretion sites in the renal tubules resulting in increased serum methotrexate and toxicity. Primarily a concern with high-dose methotrexate and thus the combination should be avoided if possible.
6. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
7. **Extravasation:** DOXOrubicin causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
8. **Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment recommended at 5 years.
9. **Neurotoxicity:** If patient experiences hearing loss or clinically/functionally significant neuropathy, discontinue CISplatin.
10. **Ototoxicity:** CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.

Contact Dr. Alannah Smerke 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(2):87-101.
2. Bleyer WA. The clinical pharmacology of methotrexate: new applications of an old drug. Cancer 1978;41(1):36- 51.
3. Marina NM, Smeland S, Bielack SS, et al. Comparison of MAPIE versus MAP in patients with a poor response to preoperative chemotherapy for newly diagnosed high-grade osteosarcoma (EURAMOS-1): an open-label, international, randomised controlled trial (AOST0331). Lancet Oncol. 2016 Oct;17(10):1396-1408.