BC Cancer Protocol Summary for Central Nervous System Prophylaxis with High Dose Methotrexate in Diffuse Large B-Cell Lymphoma

Protocol Code	*LYHDMTXPRO*
Tumour Group	*Lymphoma*
Contact Physician	*Dr. Diego Villa*
Contact Pharmacist	*Louisa Pang*

ELIGIBILITY:

1. Age: 16 y or greater
2. Performance status: ECOG 0-3
3. **Diagnosis**: biopsy-proven diffuse large B-cell lymphoma with high risk of CNS involvement, but no established CNS disease
    a. All stages of testicular DLBCL
    b. Advanced stage DLBCL with renal involvement
    c. Advanced stage DLBCL with other high-risk features for CNS relapse
4. Acceptable hematologic, renal and hepatic function

EXCLUSIONS:

1. Estimated glomerular filtration rate (GFR) or estimated creatinine clearance (CrCl) below 60 mL/min

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

N = 1.23 male
1.04 female

2. Pleural effusion, ascites, full extremity edema.
3. AST, ALT, alkaline phosphatase or total bilirubin greater than twice upper limit of normal

TESTS:

- *Baseline and Pretreatment*:
    - Baseline Only (required, but results do not have to be available to proceed with treatment; results must be checked before proceeding with cycle 2): LDH, HBsAg, HBcoreAb
    - CBC & diff, platelets, serum creatinine, electrolytes panel, ALT, bilirubin, alkaline phosphatase, LDH
    - urine pH
    - chest radiograph
    - Baseline Folstein mini mental status exam (MMSE) (see Appendix 1)
    - ECOG performance status
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- During treatment:
    - Immediately pre-methotrexate and q6h: urine pH
    - Daily every morning during methotrexate treatment: serum creatinine, electrolytes panel
    - If clinically indicated post methotrexate: daily ALT, bilirubin, alkaline phosphatase, LDH, GGT
    - **At hour 48** (from start of methotrexate infusion)**, or morning of day 3, then daily q am:** methotrexate levels (until less than 0.1 micromol/L; note date and time of withdrawal as well as start time of infusion on specimen.)
    - Folstein mini mental status exam (MMSE) at cycle 4

PREMEDICATIONS:

For methotrexate portion:

ondansetron 8 mg PO or IV before methotrexate
prochlorperazine 10 mg PO after methotrexate infusion completed and then 10 mg PO q6h PRN

SUPPORTIVE MEDICATIONS:

If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg PO daily during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive.

TREATMENT:

Patients must have GFR (or CrCl) greater than 60 mL/min and vigorous IV hydration and urine alkalinization to maintain urine pH above 7.[1]

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 7 before starting methotrexate.

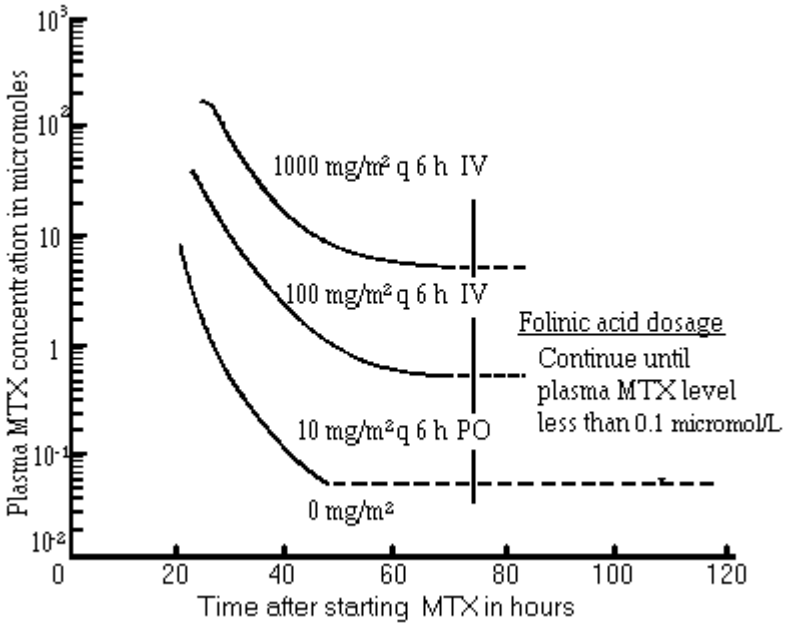
DRUG	DOSE	BC CANCER ADMINISTRATION GUIDELINES
methotrexate	3.5 grams/m^2 on day 1	IV in 1000mL NS over 4 hours See “Dose Modifications” section below.
leucovorin	25 mg q6h (start day 2)	Starting exactly 24 hours after start of methotrexate infusion; IV for 4 doses then PO until methotrexate level IS LESS THAN 0.1 micromol/L*

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

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*** CrCl

Cycles are administered every two weeks x 4 cycles

^^^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 done on day 3 is used to plot the initial slope of the curve on the Bleyer diagram below and 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**:

ANC (x10^9/L)		Platelets (x10^9/L)	Dose Modification
greater than or equal to 1.0	and	greater than or equal to 75	Proceed with treatment
less than 1.0	or	less than 75	Delay

2. **Hepatic dysfunction:** 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.

Methotrexate only:

Bilirubin (micromol/L)		***AST or ALT(units/L)***	***Dose Modification***
2 to 49			100%
50 to 85	OR	3 x ULN	75%
Greater than 85			Omit

3. **Renal Dysfunction**:

If GFR (or CrCl) less than 60 mL/min, 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*** CrCl

For methotrexate, patients must have GFR (or CrCl) greater than 60 mL/min and vigorous IV hydration and urine alkalinization to maintain urine pH above 7.[1]

4. **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. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Hepatitis B Reactivation:** All lymphoma patients should be tested for both HBsAg and HBcoreAb. If either test is positive, such patients should be treated with lamiVUDine during chemotherapy and continue for one year from treatment completion for patients who are HBsAg positive and for six months for patients who are HBcoreAb positive. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.
3. **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.
4. **Renal elimination:** Patients with elevated serum creatinine or calculated GFR (or CrCl) 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.
5. **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.

6. **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.
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Call Dr. Diego Villa 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.
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5. 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.
6. Villa D, Connors JM, Sehn LH, et al. Diffuse large B-cell lymphoma with renal involvement: outcome and risk of central nervous system relapse. Haematologica 2011;96(7):1002-07.
7. Villa D, Connors JM, Shenkier TN, et al. Incidence and risk factors for central nervous system relapse in patients with diffuse large B-cell lymphoma: the impact of the addition of rituximab to CHOP chemotherapy. Ann Oncol 2010;5(21):1046-52.
8. Lexicomp Online®, Interaction Monograph, Methotrexate/Penicillins; 25 October 2016.
9. Cheah C.Y., Herbert K.E, O'Rouke K et al. A multicenter retrospective comparison of central nervous system prophylaxis strategies among patients with high-risk diffuse large B-cell lymphoma. Br J Cancer 2014;111(6):1072-9.
10. Abramson JS, Hellmann M, Barnes JA et al. Intravenous methotrexate as central nervous system (CNS) prophylaxis is associated with a low risk of CNS recurrence in high-risk patients with diffuse large B-cell lymphoma. Cancer 2010;116(18):4283-90

APPENDIX 1:

Folstein's Mini-Mental Status Exam

1. Orientation (10 pts)
   - Time – Date, Year, Month, Day, Season
   - Place – Hospital, Floor, City, Province, Country

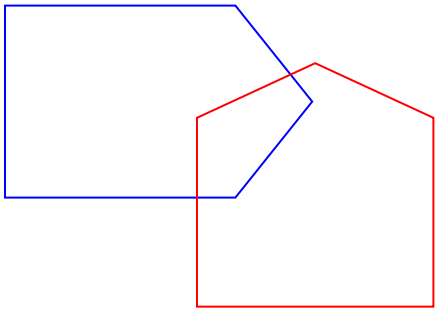
2. Registration (3 pts)
   - 3 objects – 1st repetition

3. Attention and Calculation (5 pts)
   - Serial 7's or spell "world" backwards

4. Recall (3 pts)
   - recall 3 objects

5. Language (8 pts)
   - Naming – watch and pencil (2 pts)
   - Repetition – "No if's, and's, or but's" (1 pt)
   - 3-stage command – "Take the paper in your right hand, fold it in half and put it on the floor" (3 pts)
   - Reading – "Close your eyes" (1 pt)
   - Writing – spontaneous sentence (1 pt)

6. Copying (1 pt)



TOTAL SCORE ____ / 30