BC Cancer Protocol Summary for Neoadjuvant Treatment of Urothelial Cancer using Dose-Dense Methotrexate, vinBLAStine, DOXOrubicin and CISplatin

Protocol Code	*GUBDDMVAC*
Tumour Group	*Genitourinary*
Contact Physicians	*Dr. Bernie Eigl* *Dr. Christian Kollmannsberger* *Dr Jean-Michel Lavoie*

ELIGIBILITY

Patients must have:
- Urothelial cancer
- Clinically suspected or pathologically determined T2 –T4 disease, who are planned for definitive treatment (surgery or chemo radiation), and
- No evidence of metastatic disease

Patients should have:
- ECOG performance status 0-2
- Adequate hepatic and renal function

TESTS:

- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH
- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH

PREMEDICATIONS

- On Day 2: Antiemetic protocol for highly emetogenic chemotherapy protocols (see SCNAUSEA).

- If giving CISplatin split dosing:
    - On Day 1: Antiemetic protocol for moderately emetogenic chemotherapy protocols (see SCNAUSEA).
    - On Day 2: Antiemetic protocol for highly emetogenic chemotherapy protocols (see SCNAUSEA).

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
methotrexate	30 mg/m² on Day 1	IV push
vinBLAStine	3 mg/m² on Day 2	IV in 50 mL NS over 15 minutes
DOXOrubicin	30 mg/m² on Day 2	IV push
CISplatin	70 mg/m² on Day 2	Prehydrate with 1000 mL NS over 60 minutes, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour
filgrastim (G-CSF)	5 mcg/kg/day Days 4 to 10 (or adjust as needed*)	subcutaneous

*reduce filgrastim treatment duration if ANC greater than 10 or intolerable bone pain. Filgrastim should not be stopped before the time of predicted nadir from chemotherapy.

- Repeat every 14 days x 4 cycles. Up to 6 cycles may be considered in specific cases, upon approval of Provincial GU conference.

DOSE MODIFICATIONS:

1. **Hematology**: methotrexate, vinBLAStine and DOXOrubicin

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.0	and	greater than or equal to 90	100 %
less than 1.0	or	less than 90	Delay 1 week until recovery

2. **Renal Dysfunction**: CISplatin

Creatinine Clearance (mL/min)	CISplatin dose
greater than or equal to 60	70 mg/m^2 on Day 2
45 to less than 60	35 mg/m^2 on Days 1 and 2 (same prehydration as 70 mg/m^2 dose)
less than 45	Delay 1 week

Renal dysfunction: Methotrexate

Creatinine clearance (mL/min)	Methotrexate dose
61 to 80	75%
51 to 60	70%
10 to 50	30 to 50%
less than 10	avoid

Cockcroft-Gault Formula

$$\text{GFR} = \frac{\text{N* x (140 - age in years) x wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

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

3. **Hepatic dysfunction:** Methotrexate

Bilirubin (micromol/L)		ALT (units/L)	Methotrexate Dose
less than 50	and	less than 180	100%
50 to 85	or	greater than 180	75%
greater than 85			Omit dose

PRECAUTIONS:

1. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
3. **Pulmonary Toxicity:** Acute shortness of breath may occur. Discontinue treatment if drug-induced pneumonitis is suspected.

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

REFERENCES:

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2. Plimack ER, Hoffman-Censits JH, Viterbo R, et al. Accelaerated Methotrexate, Vinblastine, Doxorubicin and Cisplatin is Safe, Effective, and Efficient Neoadjuvan Treatment for Muscle-Invasive Bladder Cancer: Results of a Multicentre Phase II Study with Molecular Correlates of Response and Toxicty. J Clin Oncol. 2014 June 20;32 (18): 1895-1901
3. Stenberg CN, de Mulder PHM, Schornagel JH, et al. Randomized Phase III Trial of High-Dose-Intesity Methotrexate, Vinblastine, Doxorubicin, and Cisplatin (MVAC) chemotherapy and Recombinant Human Granulocyte Colony-Stimulating Factor Versus Classic MVAC in Advanced Urothelial Tract Tumours: European Organization for Research and Treatment of Cancer Protocol No. 30924. J Clin Oncol 2001 May 15; 19 (10): 2638-2646
4. Van der Maase SW, Hansen SW, Roberts JT, et al. Gemcitabine and Cisplatin Versus Methotrexate, Vinblastine, Doxorubicin, and Cisplatin in Advanced or Metastatic Bladder Cancer: Results of a Large, Randomised, Multinational, Multicentre, Phase III Study. J Clin Oncol. 2000. 17 (17): 3068-3077