BC Cancer Protocol Summary for Neo-Adjuvant Therapy for Urothelial Carcinoma using CISplatin and Gemcitabine

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

ELIGIBILITY:

Patients must have:
- Muscle invasive urothelial cancer (cT2-4, N0-1), and
- Be planned for curative intent local therapy (cystectomy or trimodality therapy with surgery, radiation, chemotherapy)

Patients should have:
- ECOG performance status 0 or 1

Note: GUBDDMVAC protocol is the preferred treatment for the majority of patients. GUNAJPG is for use in patients ineligible for GUBDDMVAC (e.g., specific contraindications to methotrexate or DOXOrubicin) per physician discretion

EXCLUSIONS:

Patients must not have:
- Pure adenocarcinoma,
- Pure small-cell carcinoma (platinum and etoposide should be used, see protocol GUSCPERT),
- Poor renal function (initial creatinine clearance less than 45 mL/min by GFR measurement or Cockcroft-Gault formula)
- Contraindication for curative intent local therapy, such as major co-morbid illness

TESTS:

- Baseline: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase
- Before each treatment:
  - Day 1: CBC & Diff, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase
  - Day 8: CBC & Diff, platelets, creatinine
- Baseline imaging of bladder and pelvis

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy protocols (see protocol SCNAUSEA).

Activated: 1 Jan 2005 (as UGUNAJPG) Revised: 1 Dec 2023 (Contact physicians, eligibility, exclusions, tests and references updated, carboplatin option removed)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
gemcitabine	1250 mg/m^2/day on Days 1 and 8 (total dose per cycle = 2500 mg/m^2)	IV in 250 mL NS over 30 min
CISplatin	70 mg/m^2/day on Day 1	Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500 mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour

- Repeat every 21 days for total of two cycles prior to restaging.
- Plan for 4 cycles maximum prior to surgery or radiation, if tolerated and if no disease progression.

DOSE MODIFICATIONS:

1. **Hematology**

For gemcitabine Day 1 of each cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.0	and	greater than or equal to 100	100%
0.5 to less than 1.0	or	75 to less than 100	75%
less than 0.5	or	less than 75	***Delay****
CISplatin also delayed			

For gemcitabine Day 8 of each cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose**
greater than or equal to 1.0	and	greater than or equal to 100	100%
0.5 to less than 1.0	or	75 to less than 100	75%
less than 0.5	or	less than 75	***Omit***
****Dose adjustment only for the day of treatment the CBC is drawn**			

2. **Renal Dysfunction**

Creatinine Clearance (mL/min)	CISplatin dose	gemcitabine dose
greater than or equal to 60	70 mg/m^2 on Day 1	100%
45 to less than 60	35 mg/m^2 on Days 1 and 8 (same prehydration as 70 mg/m^2 dose)	100%
less than 45	***Delay***	***Delay/omit ****
****Delay if Day 1; if Day 8, omit if serum creatinine greater than 3 x ULN where ULN = local upper limit of normal range.***		

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.
4. **Ototoxicity**: CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.

Contact Dr. Bernie Eigl, Dr. Christian Kollmannsberger, Dr. Jean-Michel Lavoie or tumour group delegate at (604) 877-2730 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. von der Maase H, 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, randomized, multinational, multicenter, phase III study. J Clin Oncol 2000;18(17):3068-77.
2. Neoadjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis. Lancet June 7, 2003,361:1927-34.
3. Neoadjuvant cisplatin, methotrexate, and vinblastine chemotherapy for muscle-invasive bladder cancer: a randomised controlled trial. Lancet 1999; 354: 533–40.Fday 1
4. Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration. Eur Urol 2005;48(2):202-5; discussion 5-6.
5. Pfister C, Gravis G, Flechon A, et al. Multicenter randomized phase III trial of dose-dense methotrexate, vinblastine, doxorubicin, and cisplatin (dd-MVAC) or gemcitabine and cisplatin (GC) as perioperative chemotherapy for muscle-invasive bladder cancer (MIBC): Overall survival (OS) data at 5 years in the GETUG/AFU V05 VESPER trial. JCO ; 2023;41(17):LBA4507_suppl.LBA4507