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

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

ELIGIBILITY:

Patients must have:

- Urothelial cancer, clinical M0, and
  - Muscle-invasive disease (pT2 to pT4, N any), or
  - Lymph node-positive disease (pT any, N1 to N3) (providing all macroscopically abnormal nodes are resected), and
- Ability to start treatment within 90 days of radical (total) cystectomy

Patients should have:

- ECOG performance status 0 or 1

Note: Treatment with GUAJPG precludes the use of adjuvant nivolumab

EXCLUSIONS:

Patients must not have:

- Pure adenocarcinoma,
- Pure small-cell carcinoma (platinum and etoposide should be used, see protocol GUSCPERT),
- Patients with poor renal function (creatinine clearance less than 45 mL/min by GFR measurement or Cockcroft formula) unless treated with CARBOplatin,
- Major co-morbid illness, or
- Prior treatment with neoadjuvant chemotherapy

TESTS:

- Baseline: CBC & Differential, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase
- Before each treatment:
  - Day 1 only: CBC & differential, platelets, creatinine, total bilirubin, ALT, alkaline phosphatase
  - Day 8: CBC & Differential, platelets, creatinine

PREMEDICATIONS:

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

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 minutes
CISplatin	70 mg/m^2/day on Day 1	Prehydrate with 1000 mL NS over 1 hour, then CISplatin IV in 500mL NS with 20 mEq potassium chloride, 1 g magnesium sulfate, 30 g mannitol over 1 hour

- Repeat every 21 days for 4 cycles.

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 100	100%
0.5 to less than 1.0	or	75 to less than100	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 100	100%
0.5 to less than 1.0	or	75 to less than100	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 Day 1	100%
45 to less than 60	35 mg/m^2 Day 1 and Day 8 (same prehydration as 70 mg/m^2 dose)	100%
less than 45	***Delay***	***See below ****
****Delay if Day 1; if Day 8, omit if serum creatinine greater than 3 x ULN where ULN = local upper limit of normal range.***		

Alternatively, CARBOplatin may be used instead of CISplatin: When CARBOplatin is used, gemcitabine dose should be reduced:

Drug	Dose	BC Cancer Administration Guidelines
CARBOplatin	AUC 5 Day 1 only Dose = AUC x (GFR* +25)	IV in 250 mL NS over 30 minutes
gemcitabine	1000 mg/m^2/day on Days 1 and 8 (total dose per cycle = 2000 mg/m^2)	IV in 250 mL NS over 30 minutes

* *Measured GFR* (e.g. nuclear renogram) is preferred whenever feasible, *particularly* in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, etc.). The lab reported GFR (MDRD formula) may be used as an alternative to the Cockcroft-Gault estimate of GFR; the estimated GFR reported by the lab or calculated using the Cockcroft-Gault equation should be capped at 125 mL/min when it is used to calculate the initial carboplatin dose. When a nuclear renogram is available, this clearance would take precedence.

Cockcroft-Gault Formula

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

Note: The *same* method of estimation should be used throughout the treatment course (i.e. if lab reported GFR was used initially, this should be used for dosing in all subsequent cycles and not the Cockcroft-Gault estimate).

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

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. Stockle M, Meyenburg W, Wellek S, et al. Advanced bladder cancer (stages pT3b, pT4a, pN1 and pN2): improved survival after radical cystectomy and 3 adjuvant cycles of chemotherapy. Results of a controlled prospective study. Journal of Urology 1992;148(2 Pt 1):302-6; discussion 6-7.
3. Adjuvant chemotherapy in invasive bladder cancer: a systematic review and meta-analysis of individual patient data Advanced Bladder Cancer (ABC) Meta-analysis Collaboration. Eur Urol 2005;48(2):189-99; discussion 99-201.
4. Birtle A, Johnson M, Chester J, et al. Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. Lancet. 2020 Apr 18;395 (10232): 1268-1277.