BC Cancer Protocol Summary for Palliative Therapy for Urothelial Carcinoma Using CISplatin and Gemcitabine

Protocol Code	*GUAVPG*
Tumour Group	*Genitourinary*
Contact Physicians	*Dr. Bernie Eigl* *Dr. Christian Kollmannsberger*

ELIGIBILITY:

- Advanced urothelial carcinoma
- ECOG performance status 0, 1 or 2

EXCLUSIONS:

- Pure squamous, adenocarcinoma or small-cell carcinoma
- Patients with poor renal function (creatinine clearance less than 60 mL/min by GFR measurement or Cockcroft formula) unless treated with CARBOplatin
- Major co-morbid illness

TESTS:

- Baseline: CBC & differential, platelets, creatinine, Alk Phos, ALT, bilirubin
- Prior to each treatment:
  - Days 1: CBC & differential, platelets, creatinine, ALT, Alk Phos, LDH, bilirubin
  - 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 min
CISplatin	70 mg/m^2/day on day 1 OR 35 mg/m^2/day on days 1 and 2 (or days 1 and 8)	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 to two cycles beyond best response (maximum 6 cycles)*.
Discontinue if no response after 2 cycles.
*No Compassionate Access Program (CAP) approval required to retreat a patient with worsening disease. Patient must have had lasting response from initial therapy, continue to have good performance status and adequate renal function.
Note: A growing international consensus is recommending that the 28 day CISplatin and gemcitabine cycle be replaced with a 21 day cycle that delivers the same dose of CISplatin on day 1 and gemcitabine 1250 mg/m² on days 1 and 8.

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	and	greater than 100	100%
0.5 to 0.99	or	75 to 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	and	greater than 100	100%
0.5 to 0.99	or	75 to 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 59	35 mg/m^2 on Days 1 and 2 OR 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 CISplatin.		

Alternatively, CARBOplatin may be used instead of CISplatin:
(See table below for modified gemcitabine dosing)

DRUG	DOSE	BC Cancer Administration Guidelines
CARBOplatin	AUC 5 DAY 1 only Dose = AUC x (GFR* +25)	IV in 100 to 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

When CARBOplatin is used, gemcitabine dose should be reduced:

DRUG	DOSE	BC Cancer Administration Guidelines
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 min

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.

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

References:

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.