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*
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ELIGIBILITY:

- Urothelial bladder cancer, clinical N0 M0
- Planned cystectomy
- Muscle invasive disease
- ECOG performance status 0 or 1

EXCLUSIONS:

- Pure squamous, adenocarcinoma or small-cell carcinoma
- Patients with poor renal function (initial creatinine clearance less than 60 ml/min by GFR measurement or Cockcroft formula)
- Major co-morbid illness; non-surgical candidate
- Significant hearing impairment

TESTS:

- Baseline: CBC & differential, platelets, creatinine, bilirubin, ALT, alk, phos
- Before each treatment:
  - Days 1: CBC & differential, platelets, creatinine, bilirubin, ALT, alk, phos
  - Day 8: CBC & differential, platelets, creatinine
- Baseline imaging of bladder and pelvis

PREMEDICATIONS:

- Antiemetic protocol for high moderate 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	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, if tolerated and if no disease progression.

Activated: 1 Jan 2005 (as UGUNAJPG) Revised: 1 Apr 2018 (Test, institutional name, dose modifications, contact physician)

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 <u>serum</u> 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 min
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

* *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.

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:

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.