BC Cancer Protocol Summary for Neoadjuvant Treatment of Esophageal and Gastroesophageal Carcinomas Using CARBOplatin, PACLitaxel and Radiation Therapy

Protocol Code:	*GIENACTRT*
Tumour Group:	*Gastrointestinal*
Contact Physicians:	*GI Systemic Therapy*

ELIGIBILITY:
- Resectable esophageal or gastroesophageal carcinoma.
- Any age – patients over 79 to be assessed individually
- ECOG 0 – 2

EXCLUSIONS:
- Distant metastases
- AST and/or ALT greater than 10 times the Upper Limit of Normal
- Total bilirubin greater than 128 micromol/L
- Weight loss greater than10%
- Tumour length greater than 8 cm

RELATIVE CONTRAINDICATIONS:
- Peripheral neuropathy Grade 2 or higher
- Prior severe arthromyalgia unresponsive to treatment

TESTS:
- Baseline: CBC & diff, platelets, creatinine, bilirubin, ALT. Optional : camera nuclear renogram for GFR, CEA, CA 19-9.
- Prior to each treatment (weekly): CBC & diff, platelets, creatinine.
- If clinically indicated: bilirubin, ALT, magnesium.

PREMEDICATIONS:
- **PACLitaxel must not be started unless the following drugs have been given :**

  45 minutes prior to PACLitaxel:
  - dexamethasone 10 mg IV in 50 mL NS over 15 minutes

  30 minutes prior to PACLitaxel:
  - diphenhydrAMINE 25 mg IV in NS 50 mL over 15 minutes and famotidine 20 mg IV in NS 100 mL over 15 minutes (Y-site compatible)

- NOTE: If no PACLitaxel hypersensitivity reaction occurs, no premedications may be needed for subsequent PACLitaxel doses and may be omitted at physician's discretion..
- NOTE: If no PACLitaxel hypersensitivity reaction occurs, dexamethasone 8 mg PO may be given (pre-CARBOplatin) in place of the regimen in the first bullet point above.
- If hypersensitivity reactions occur, premedications for re-challenge include dexamethasone 20 mg PO given 12 hours and 6 hours prior to treatment, plus IV premedications given 30 minutes prior to PACLitaxel: dexamethasone 10 mg, diphenhydrAMINE 25 mg, and H_2-antagonist (e.g., famotidine 20 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- ondansetron 8 mg po 30 minutes pre-CARBOplatin.

TREATMENT

Chemotherapy (give PACLItaxel first):

Drug	Starting Dose	BC Cancer Administration Standard
PACLitaxel	50 mg/m^2 once weekly	IV in NS 100 to 250 mL over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
CARBOplatin	Dose = AUC 2 x (GFR + 25) once weekly	IV in NS 100 to 250 mL over 30 minutes

Repeat weekly for 5 weeks concurrent with radiation therapy (RT), starting the first day of RT.

Measured GFR (e.g. nuclear renogram) is preferred in circumstances of co-morbidity that could affect renal function (third-space fluid accumulations, hypoproteinemia, potentially inadequate fluid intake, age greater than 70, 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

$$\text{CrCl} = \frac{\text{N (140-age) x weight (kg)}}{\text{serum creatinine (micromol/L)}}$$

Where N = 1.04 for females, and 1.23 for males

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).

NOTE: Recalculate GFR if, at a point of checking, creatinine increases by greater than 20% or rises above the upper limit of normal (See Dose Modifications 4. Renal Dysfunction)

Radiation Therapy:
41.4 Gy in 23 fractions, 5 days per week.

DOSE MODIFICATIONS:

1. **Hematology**:

   On treatment days 1, 8, 15, 22 and 29:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Doses (both drugs)
Greater than or equal to 1.0	and	Greater than or equal to 50	100%
Less than 1.0	and/or	Less than 50	Delay chemotherapy for 1 week until recovery above these values

2. **Arthralgia and/or myalgia**: If arthralgia and/or myalgia of grade 2 (moderate) or higher was not adequately relieved by NSAIDs or acetaminophen with codeine (e.g., TYLENOL#3®), a limited number of studies report a possible therapeutic benefit using:
   - predniSONE 10 mg PO bid x 5 days starting 24 hours post-PACLitaxel
   - gabapentin 300 mg PO on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 5 to 15 days (based on duration of arthromyalgia)
3. **Neuropathy**: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
4. **Renal dysfunction**: If significant increase (greater than 20% or rises above the upper limit of normal) in creatinine, recheck/recalculate GFR and recalculate CARBOplatin dose using new GFR.
5. **Hepatic dysfunction**: Dose reduction may be required for PACLitaxel (see BC Cancer Drug Manual).

PRECAUTIONS:

1. **Hypersensitivity**: Reactions are common. See BC Cancer Hypersensitivity Guidelines

Mild symptoms (e.g., mild flushing, rash, pruritus)	▪ Complete PACLitaxel infusion. Supervise at bedside ▪ No treatment required
Moderate symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension	▪ Stop PACLitaxel infusion ▪ Give IV diphenhydrAMINE 25 to 50 mg and hydrocortisone IV 100 mg ▪ After recovery of symptoms resume PACLitaxel infusion at 20 mL/h for 5 minutes, 30 mL/h for 5 minutes, 40 mL/h for 5 minutes, then 60 mL/h for 5 minutes. If no reaction, increase to full rate. ▪ If reaction recurs, discontinue PACLitaxel therapy
Severe symptoms (i.e. *one* or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	▪ Stop PACLitaxel infusion ▪ Give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ Discontinue PACLitaxel therapy

2. **Extravasation**: PACLitaxel causes pain and may, rarely, cause tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Drug Interactions**: PACLitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Call the GI Systemic Therapy physician at your regional cancer centre or the GI Systemic Therapy Chair Dr. Janine Davies at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

REFERENCES

Van der Gaast, A. V., et al. Effect of preoperative concurrent chemoradiotherapy on survival of patients with resectrable esophageal or esophagogastric junction cancer: Results from a multicenter randomized phase III study. J Clin Oncol 28:15s, 2010 (suppl; abstr 4004)