BC Cancer Protocol Summary for NEOAdjuvant Therapy for Triple Negative Breast Cancer using Dose Dense Therapy: Carboplatin and Weekly PACLitaxel Followed by DOXOrubicin and Cyclophosphamide

***Protocol Code**:* *BRLACTWACG*

***Tumour Group**:* *Breast*

***Contact Physician**:* *Dr. Stephen Chia*

ELIGIBILITY:
A number of studies suggest that the schedule of delivery of PACLitaxel is important in maximizing efficacy. The preferred delivery method of PACLitaxel before AC chemotherapy is either every two weeks with filgrastim (G-CSF) (see protocol BRLATACG) or weekly for 12 weeks, as described in this protocol.

- Patients less than or equal to 65 years of age or fit patients greater than 65 years of age.
- Previously untreated triple negative breast cancer patients with any node positive breast cancer or tumour size ≥ 2.5 cm with clinically negative nodes (Stage IIA or greater).
- Filgrastim (G-CSF) is not covered as a benefit at BC Cancer

EXCLUSIONS:
- Severe cardiovascular disease with LVEF less than 45%
- AST and/or ALT greater than 3X ULN the Upper Limit of Normal (ULN)
- total bilirubin greater than 1.5X ULN (except for known Gilbert's syndrome)

TESTS:
- Baseline: CBC & diff, platelets, bilirubin, ALT, creatinine,
- Baseline if clinically indicated: alk phos, LDH, GGT
- Before each treatment: CBC & diff, platelets, creatinine (creatinine before each carboplatin treatment only)
- If clinically indicated: bilirubin, ALT

PREMEDICATIONS:
- **For the 4 cycles (=12 weeks) of PACLitaxel: 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)
- If no PACLitaxel infusion reactions occur, no premedications may be needed for subsequent PACLitaxel doses and may be omitted at physician's discretion.
- If infusion 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, diphehydrAMINE 25 mg, and H_2-antagonist (e.g., famotidine 20 mg). If no infusion reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- ondansetron 8 mg po 30 minutes pre-CARBOplatin

- **For the 4 cycles of DOXOrubicin and cyclophosphamide**: Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

TREATMENT:

- 4 consecutive cycles of PACLitaxel and CARBOplatin (Cycles 1 to 4)

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel	80 mg/m^2 on Days 1, 8 and 15	IV in 100 to 500 mL NS over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
CARBOplatin	AUC 6 or 5 or 4 x (GFR + 25) on Day 1	IV in 100 to 250 mL NS over 30 minutes

- Cycle length = 3 weeks, repeat every 21 days for 4 cycles (= 12 weeks total), followed by
- 4 consecutive cycles of DOXOrubicin and cyclophosphamide (Cycles 5 to 8)
- Cycle 5 to start on week 13

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	60 mg/m²	IV push
cyclophosphamide	600 mg/m²	IV in 100 to 250* mL NS over 20 min to 1 hour
filgrastim (G-CSF)	5 mcg/kg/day Days 3 to 10 (or adjust as needed)**	SC

*Use 250 mL for dose greater than 1000 mg
reduce filgrastim treatment duration if ANC greater than 10 or intolerable bone pain. Filgrastim **should not be stopped before the time of the predicted nadir from chemotherapy.

- Repeat every 14 days for 4 cycles

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

$$GFR = \frac{1.04 \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

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).

DOSE MODIFICATIONS:

1. **Hematological**

For cycles of PACLitaxel and CARBOplatin only:

- Applicable for all days of treatment (i.e. day 1 for CARBOplatin and days 1, 8, 15 for PACLitaxel)

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (both drugs)
Greater than or equal to 1.5	and	Greater than or equal to 90	100%
1.0 to less than 1.5*	or	70 to less than 90	75%
Less than 1.0	or	Less than 70	Delay** and reduce next dose level or add filgrastim

* if ANC 1.0 to less than 1.5 and patient fit and well can consider full dose of PACLitaxel 80 mg/m^2 at discretion of physician

**If repeated delays or dose reductions, consider reducing CARBOplatin to AUC of 5 from 6, or 4 from 5

For cycles of DOXOrubicin and cyclophosphamide only:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (both drugs)
Greater than or equal to 1.0	and	Greater than or equal to 100	100%
Less than 1.0	and	Greater than or equal to 100	delay for 1 week (or longer if needed), then give 100% dose if ANC greater than 1 and platelets greater than or equal to 100. Give filgrastim days 3 to 13 for remaining cycles.
Greater than or equal to 1.0	and	Less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1 and platelets greater than or equal to 100
Less than or equal to 1.0		Less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1 and platelets greater than or equal to 100

2. Non-Hematological Toxicity

Grade	Dose
Grade 2 motor or sensory neuropathy	Decrease dose of paclitaxel by 10 mg/m^2
All other clinically significant grade 2 non-hematological toxicity	Hold treatment until toxicity resolved to less than or equal grade 1 Decrease subsequent doses by 10 mg/m^2
Greater than or equal to Grade 3	Discontinue treatment

3. **Hepatic dysfunction**:

For Cycles 1 to 4: Reduce PACLitaxel dose:

ALT		Total bilirubin	Dose (mg/m^2)
less than 3 x ULN	and	less than or equal to 1.25 x ULN	80
less than 3 x ULN	and	1.26 to 2 x ULN	60
less than 3 x ULN	and	2.01 to 3 x ULN	40
greater than or equal to 3 x ULN	and/or	greater than 3 x ULN	not recommended

ULN = upper limit of normal

For Cycles 5 to 8: Dose modifications required for DOXOrubicin. Refer to BC Cancer Drug manual.

4. **Renal dysfunction:** Use nuclear renogram or predictive formula to calculate cycle 1 dose, as detailed above. Consider re-calculation of dose if serum creatinine changes ± 20% from baseline. Dose modification may be required for Cyclophosphamide. Refer to BC Cancer Drug Manual.

5. Arthralgia and/or myalgia: If arthralgia and/or myalgia of grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (e.g., TYLENOL #3®), a limited number of studies report a possible therapeutic benefit using:
   - gabapentin 300 mg po on day before chemotherapy, 300 mg bid on treatment day, then 300 mg tid x 7 to 10 days

   If arthralgia and/or myalgia persist, reduce subsequent PACLitaxel doses to 65 mg/m^2.

6. Neuropathy: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).
7. **Gastrointestinal toxicity:** If greater than or equal to grade 3 mucositis occurs, PACLitaxel and CARBOplatin should be withheld until resolution to less than or equal to grade 1, then reinstituted at 80% of previous dose.

PRECAUTIONS:

1. **Infusion-related reactions**: Reactions to PACLitaxel are common. See BC Cancer Infusion-Related Reactions 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**: DOXOrubicin and PACLitaxel causes pain and 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.

Call Dr. Stephen Chia or tumour group delegate at 604-877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References

1. von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014;15(7):747-56.
2. Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33(1):13-21.
3. Rugo HS, Olopade OI, DeMichele A, et al. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med;375(1):23-34.