

BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Breast Cancer using Dose Dense Therapy: DOXOrubicin and Cyclophosphamide followed by PACLitaxel

Protocol Code

BRAJACTG

Tumour Group

Breast

Contact Physician

Dr. Nathalie LeVasseur

ELIGIBILITY:

- Patients with 1 or more axillary lymph node metastasis(es), **or** node negative but with high risk of recurrence (see Cancer Management Guidelines for categories of risk)

Note:

- Filgrastim (G-CSF) is not covered as a benefit at the BC Cancer
- A number of studies suggest that the schedule of delivery of PACLitaxel is important in maximizing efficacy. The preferred delivery method of PACLitaxel after AC chemotherapy is either weekly for 12 weeks (see protocol BRAJACTW) or every two weeks with G-CSF, as described in this protocol.
- BC Cancer Compassionate Access Program (CAP) approval is not required to change from BRAJACTG to BRAJACTW for patient tolerance

EXCLUSIONS:

- Pregnancy
- Congestive heart failure (LVEF less than 45%) or other significant heart disease
- Known hypersensitivity to E. coli derived products

TESTS:

- Baseline: CBC & Diff, total bilirubin, ALT (ALT and total bilirubin should be measured prior to first cycle of AC and first cycle of PACLitaxel)
- Before each treatment: CBC & Diff
- If clinically indicated: creatinine; MUGA scan or echocardiogram, total bilirubin, ALT

PREMEDICATIONS:

- For the 4 cycles of DOXOrubicin and cyclophosphamide: Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- For the 4 cycles of PACLitaxel: **PACLitaxel must not be started unless the following drugs have been given:**
 - 45 minutes prior to PACLitaxel give dexamethasone 20 mg IV in NS 50 mL over 15 minutes
 - 30 minutes prior to PACLitaxel give diphenhydrAMINE 50 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 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 20 mg, diphenhydramine 50 mg, and H2-antagonist (e.g., famotidine 20 mg). If no hypersensitivity reactions occur, standard premedications (see above) will be used for subsequent PACLitaxel doses.
- Additional anti-emetics are not usually required

TREATMENT:

Four consecutive cycles of DOXOrubicin and cyclophosphamide

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	60 mg/m ²	IV push
cyclophosphamide	600 mg/m ²	IV in NS 100 to 250* mL over 20 mins to 1 hour
filgrastim (G-CSF)	5 mcg/kg/day Days 3 to 10 (or adjust as needed**)	subcutaneous

*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 x 4 cycles.

Four consecutive cycles of PACLitaxel to start **14 days after** final cycle of DOXOrubicin and cyclophosphamide

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel	175 mg/m ²	IV in 250 to 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)
filgrastim (G-CSF)	5 mcg/kg/day Days 3 to 10 (or adjust as needed**)	subcutaneous

- Repeat cycle every 14 days x 4 cycles

**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

DOSE MODIFICATIONS:

1. Hematological (for Day 1 counts)

Table 1.

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (all 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

- Febrile neutropenia:** 75% of dose for current and subsequent cycles.
- Renal dysfunction:** Dose modification may be required for cyclophosphamide. Refer to BC Cancer Drug Manual.
- Hepatic dysfunction:** Dose modification required for DOXOrubicin and for PACLitaxel. Refer to BC Cancer Drug Manual.
- Arthralgia and/or myalgia:** If arthralgia and/or myalgia from PACLitaxel of grade 2 (moderate) or higher is not relieved by adequate doses of NSAIDs or acetaminophen with codeine (TYLENOL #3®) a limited number of studies report a possible therapeutic benefit from the following:
 - prednisone 10 mg PO BID x 5 days starting 24 hours post PACLitaxel
 - gabapentin 300 mg PO on day prior to PACLitaxel, 300 mg PO BID on treatment day and then 300 mg PO TID x 7 to 10 days
- Neuropathy:** Dose modification or discontinuation for PACLitaxel may be required. Refer to BC Cancer Drug Manual.

PRECAUTIONS:

- Febrile Neutropenia:** Risk of febrile neutropenia is greater than 20% without the use of filgrastim. Mandatory filgrastim reduces the risk of febrile neutropenia. Febrile neutropenia can result in patient harm, treatment delays, and hospitalization. Fever or other evidence of infection must be assessed promptly and treated aggressively.
- Extravasation:** DOXOrubicin and PACLitaxel may cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
- Cardiac Toxicity:** DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction. Cardiac assessment recommended if lifelong dose of 450 mg/m² to be exceeded. Refer to BC Cancer Drug Manual.

4. **Hypersensitivity:** Reactions are common with PACLitaxel. Refer to BC Cancer [SCDRUGRX](#).

<u>Mild</u> symptoms (e.g. mild flushing, rash, pruritus)	<ul style="list-style-type: none"> ▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
<u>moderate</u> symptoms (e.g. moderate rash, flushing, mild dyspnea, chest discomfort, mild hypotension)	<ul style="list-style-type: none"> ▪ stop PACLitaxel infusion ▪ give IV diphenhydrAMINE 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
<u>severe</u> symptoms (i.e. <u>one</u> or more of respiratory distress requiring treatment, generalised urticaria, angioedema, hypotension requiring therapy)	<ul style="list-style-type: none"> ▪ stop PACLitaxel infusion ▪ give IV antihistamine and steroid as above. Add epinephrine or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

Alternative therapy with protocol BRAJPN is available for moderate to severe hypersensitivity reaction that occurs despite premedications, or in those patients who cannot be managed with premedications due to a strong contraindication.

Call Dr. [Nathalie LeVasseur](#) or tumour group delegate at **(604) 930-2098** or **1-800-663-3333** with any problems or questions regarding this treatment program.

References:

1. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of nod-positive primary breast cancer: first report of intergroup trial C9741/cancer and leukemia group b trial 9741. J Clin Oncol 2003; 21:1431-1439.