BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Early Breast Cancer Using DOXOrubicin and Cyclophosphamide followed by Weekly PACLitaxel

***Protocol Code**:*	*BRAJACTW*
***Tumour Group**:*	*Breast*
***Contact Physician**:*	*Dr. Nathalie LeVasseur*

ELIGIBILITY:

- Neoadjuvant or adjuvant treatment for 1 or more axillary lymph node metastasis(es), ***or*** node negative but with high risk of recurrence

Note:

- 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 every two weeks with G-CSF (see protocol BRAJACTG) or weekly for 12 weeks, as described in this protocol.
- BC Cancer Compassionate Access Program (CAP) approval is not required to change from BRAJACTG to BRAJACTW for patient tolerance

Note:

- Primary prophylaxis with G-CSF is not mandatory, but may be considered if patient has one or more of the following risk factors:
    - Prior chemotherapy or radiation therapy
    - Persistent neutropenia
    - Recent surgery and/or open wounds
    - Liver dysfunction
    - Renal dysfunction
    - Older than 65 years of age and receiving full chemotherapy dose intensity

EXCLUSIONS:

- Pregnancy
- Severe cardiovascular disease with LVEF less than 55%
- AST and/or ALT greater than 10 times the Upper Limit of Normal (ULN)
- total bilirubin greater than 128 micromol/L

TESTS:

- Baseline and prior to Cycle 5: CBC & Diff, total bilirubin, ALT
- Baseline, if clinically indicated: creatinine, alkaline phosphatase, LDH, GGT, MUGA scan or echocardiogram
- Before each treatment: CBC & Diff
- If clinically indicated: total bilirubin, ALT, creatinine
- Cycles 1 to 4, If clinically indicated: MUGA scan or echocardiogram

PREMEDICATIONS:

- For the 4 cycles of DOXOrubicin and cyclophosphamide: Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- **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 20 mg, diphenhydrAMINE 50 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.
- Additional antiemetics not usually required.

TREATMENT:

- 4 consecutive cycles of DOXOrubicin and cyclophosphamide

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

*Use 250 mL for dose greater than 1000 mg

Repeat every 21 days for 4 cycles, followed by:

- 4 consecutive cycles of PACLitaxel

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel	80 mg/m² weekly	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)

- Cycle length = 3 weeks, repeat every 21 days for 4 cycles (= 12 weeks total)

DOSE MODIFICATIONS:

1. **Hematological**

   For cycles of DOXOrubicin and cyclophosphamide only:

ANC (x10^9/L)		Platelets (x10^9/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

For cycles of PACLitaxel only:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose	Dose after Neutropenic Sepsis on PACLitaxel
Greater than or equal to 1.0	and	Greater than or equal to 90	80 mg/m^2	65 mg/m^2
Less than 1.0	or	Less than 90	Contact Physician: Delay treatment. Physician may choose to reduce next dose to 65 mg/m^2 or add filgrastim (if not already using)	delay

2. **Non-Hematological Toxicity**

Grade	Dose
Grade 2 motor or sensory neuropathy	Decrease dose by 10 mg/m^2
All other 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: Dose modifications required for DOXOrubicin. Refer to BC Cancer Drug manual.

For Cycles 5-8: Reduce PACLitaxel dose:

ALT		Total bilirubin	Dose (mg/m^2)
less than 10 x ULN	and	less than or equal to 1.25 x ULN	80
less than 10 x ULN	and	1.26 to 2 x ULN	60
less than 10 x ULN	and	2.01 to 5 x ULN	40
greater than or equal to 10 x ULN	and/or	greater than 5 x ULN	not recommended

ULN = upper limit of normal

4. **Renal dysfunction:** 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 (eg, 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 65mg/m^2.
6. **Neuropathy:** Dose modification or discontinuation may be required (see BC Cancer Drug Manual).

PRECAUTIONS:

1. **Infusion-related reactions**: Reactions to PACLitaxel are common. See BC Cancer SCDRUGRX.

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 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

   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.
2. **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **Febrile Neutropenia**: Risk of febrile neutropenia is 10 to 20%. If a patient has additional risk factors outlined in Eligibility Note above, risk of febrile neutropenia may be considered to be greater than 20%; consider prophylactic filgrastim per discretion of the treating physician. Febrile neutropenia can result in serious patient harm, treatment delays, and hospitalization. Fever or other evidence of infection must be assessed promptly and treated aggressively.

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 M, 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 node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003;21:1431-9.
2. Sparano JA, Wang M, Martino S, et al. Phase III study of doxorubicin-cyclophosphamide followed by paclitaxel or docetaxel given every 3 weeks or weekly in operable breast cancer: results of Intergroup Trial E1199. J Clin Oncol (Meeting Abstracts) June 2007;25(18_suppl): abstr 516.