

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

Protocol Code

BRAJACT

Tumour Group

Breast

Contact Physician

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ELIGIBILITY:

A number of studies jointly suggest that, when PACLitaxel is chosen for adjuvant therapy, it may be more efficacious to administer it on a dose-dense or weekly protocol. For this reason, BRAJACT, given at standard 3 weekly intervals, is not generally a preferred regimen, unless individual patient circumstances dictate that this regimen is the most safe and feasible treatment selection for a patient.

- Neoadjuvant or adjuvant treatment for 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:

- 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%

TESTS:

- Baseline: CBC & Diff, total bilirubin, ALT (ALT and bilirubin should be measured prior to first cycle of AC and first cycle of PACLitaxel)
- Baseline, if clinically indicated: creatinine, echocardiogram, MUGA
- 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)
 - additional anti-emetics are not usually required
- 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.

TREATMENT:

- 4 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 min to 1 hour

*Use 250 mL for dose greater than 1000 mg

Repeat every 21 days x 4 cycles.

- 4 consecutive cycles of PACLitaxel to start **21 days after** final cycle of DOXOrubicin and cyclophosphamide

Drug	Dose	BC Cancer Administration Guideline
PACLitaxel	175 mg/m ²	IV in NS 250 to 500 mL over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.2 micron in-line filter)

Repeat cycle every 21 days x 4 cycles

DOSE MODIFICATIONS:

1. Hematological (for Day 1 counts)

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 less than 90	75%
Less than 1.0	or	Less than 70	delay

For cycles of PACLitaxel only:

ANC (x10 ⁹ /L)		Platelets (x10 ⁹ /L)	Dose (PACLitaxel)
Greater than or equal to 1.5	and	Greater than or equal to 90	175 mg/m ²
1.0 to less than 1.5	or	70 less than 90	150 mg/m ²
Less than 1.0	or	Less than 70	delay

- 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 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.

2. **Extravasation:** DOXOrubicin and PACLitaxel causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
3. **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.

<i>Mild</i> symptoms (e.g. mild flushing, rash, pruritus)	<ul style="list-style-type: none"> ▪ complete PACLitaxel infusion. Supervise at bedside ▪ no treatment required
<i>moderate</i> 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
<i>severe</i> 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. Stephen Chia or tumour group delegate at (604) 930-2098 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Henderson IC, Beryy D, Demetri G, Cirrincione C et al. Improved disease-free (DFS) and overall survival (OS) from the addition of sequential paclitaxel (T) but not from the escalation of doxorubicin (A) dose level in the adjuvant chemotherapy of patients (PTS) with node-positive primary breast cancer (BC). Proc Am Soc Clin Oncol 1998;17:101a.
2. Citron, M.L.; Berry, D.A.; Cirrincione, C.; 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 21(8), 1431-1439, 2003.
3. Burnell M, Levine M, Chapman JA et al. [53] A randomized trial of CEF versus dose dense EC followed by paclitaxel versus AC followed by PACLitaxel in women with node positive or high risk node negative breast cancer, NCIC CTG MA.21: Results of an interim analysis. Breast Cancer Research and Treatment, Vol. 100, Supplement 1, 2006
4. 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. Abst. 516, ASCO annual meeting, June 2007