

BCCA Protocol Summary for NEOAdjuvant Therapy for Breast Cancer using Dose Dense Therapy: PACLitaxel followed by DOXOrubicin and Cyclophosphamide

Protocol Code

BRLATACG

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 G-CSF as described in this protocol or weekly for 12 weeks(see protocol BRLATWAC).

- Locally advanced and inflammatory breast cancer in patients less than or equal to 65 years of age or fit patients greater than 65 years of age.
- Filgrastim (G-CSF) is not covered as a benefit at the BCCA

EXCLUSIONS:

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

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, AST, ALT, creatinine
- Before each treatment: CBC & diff, platelets
- If clinically indicated at anytime: creatinine, bilirubin, AST, ALT, MUGA scan or echocardiogram

PREMEDICATIONS:

- 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 and ranitidine 50 mg IV in 50 mL over 20 minutes (compatible up to 3 hours when mixed in bag)
 - additional anti-emetics are not usually required
- For the 4 cycles of DOXOrubicin and cyclophosphamide: Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

TREATMENT:

Four consecutive cycles of PACLitaxel (Cycles 1 to 4)

Drug	Dose	BCCA Administration Guideline
PACLitaxel	175 mg/m ²	IV in 500 mL NS over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller in-line filter)
filgrastim (G-CSF)	5 mcg/kg/day Days 3 to 10 (or adjust as needed**)	SC

**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 cycle every 14 days x 4 cycles, followed by

Four consecutive cycles of DOXOrubicin and cyclophosphamide (Cycles 5 to 8) to start **14 days after** final cycle of PACLitaxel

Drug	Dose	BCCA 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**)	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 x 4 cycles.

DOSE MODIFICATIONS:

1. Hematological (for Day 1 counts)

ANC (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose (all drugs)
Greater than or equal to 1	and	Greater than or equal to 100	100%
Less than 1	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	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		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:** Consider 75% of dose for current and subsequent cycles.
- Renal dysfunction:** Dose modification may be required for cyclophosphamide. Refer to BCCA Cancer Drug Manual.
- Hepatic dysfunction:** Dose modification required for DOXOrubicin and for PACLitaxel. Refer to BCCA 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 BCCA Cancer Drug Manual.

PRECAUTIONS:

- Neutropenia:** 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 BCCA 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 BCCA Cancer Drug Manual.

4. **Hypersensitivity:** Reactions are common with PACLitaxel. Refer to BCCA Hypersensitivity Guidelines.

<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 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
<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 <u>epinephrine</u> or bronchodilators if indicated ▪ discontinue PACLitaxel therapy

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.

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References:

1. Citron ML, Berry DA, Cirincione 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.
2. Earl H, et al. Effects of the addition of gemcitabine and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label 2x2 factorial randomized phase 3 trial. Lancet Oncol 2014;15:201-212.
3. Bines J, Earl H, Buzaid AC, Saad ED. Anthracyclines and taxanes in the neo/adjuvant treatment of breast cancer: does the sequence matter? Ann Oncol 2014;25(6):1079-85.