BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer using DOXOrubicin and Cyclophosphamide followed by PACLitaxel

Protocol Code *BRAJACT*

Tumour Group *Breast*

Contact Physician *Dr. Stephen Chia*

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.

- 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)

EXCLUSIONS:

- Pregnancy
- Severe cardiovascular disease with LVEF less than 55%

TESTS:

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

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 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

TREATMENT:

- 4 consecutive cycles of DOXOrubicin and cyclophosphamide

Drug	Dose	BCCA Administration Guideline
DOXOrubicin	60 mg/m²	IV push
cyclophosphamide	600 mg/m²	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	BCCA Administration Guideline
PACLitaxel	175 mg/m²	IV in NS 500 mL over 3 hours (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller 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 90	100%
1 to 1.49	or	70 to 90	75%
Less than 1	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 90	175 mg/m^2
1 to 1.49	or	70 to 90	150 mg/m^2
Less than 1	or	Less than 70	delay

2. **Renal dysfunction:** Dose modification may be required for cyclophosphamide. Refer to BCCA Cancer Drug Manual.
3. **Hepatic dysfunction:** Dose modification required for DOXOrubicin and for PACLitaxel. Refer to BCCA Cancer Drug Manual.
4. **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
5. **Neuropathy:** Dose modification or discontinuation for PACLitaxel may be required. Refer to BCCA Cancer Drug Manual.

PRECAUTIONS:

1. **Neutropenia**: 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 BCCA 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/m^2 to be exceeded. Refer to BCCA Cancer Drug Manual.
4. **Hypersensitivity**: Reactions are common with PACLitaxel. Refer to BCCA Hypersensitivity 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

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. 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