

BC Cancer Protocol Summary for Adjuvant therapy for Early Breast Cancer Using DOXOrubicin and Cyclophosphamide Followed by Weekly PACLitaxel

Protocol Code:
Tumour Group:
Contact Physician:

BRAJACTW
Breast
Dr. Caroline Lohrisch

ELIGIBILITY:

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.

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

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, platelets, bilirubin, ALT
- **Baseline if clinically indicated: alk phos, LDH, GGT**
- Before each treatment: CBC & diff, platelets
- If clinically indicated: bilirubin, ALT, creatinine

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
 - diphenhydramine 25 mg IV and ranitidine 50 mg IV in 50 mL NS over 20 minutes (compatible up to 3 hours when mixed in bag)
- If no PACLitaxel hypersensitivity reactions occur, no premedications may be needed for subsequent PACLitaxel doses and may be omitted at physician's discretion.
- 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 10 mg, diphenhydramine 25 mg, and H₂-antagonist (e.g., ranitidine 50 mg). If no hypersensitivity 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/m ²	IV push
cyclophosphamide	600 mg/m ²	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/m ² weekly	IV in 250 mL* NS over 1 hour (use non-DEHP bag and non-DEHP tubing with 0.22 micron or smaller in-line filter)

*Use 100 mL for dose less than 87 mg

- 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 1.5	and	Greater than or equal to 90	80 mg/m ²	65 mg/m ²
1.0 to less than 1.5	or	70 to less than 90	65 mg/m ²	50 mg/m ²
Less than 1.0	or	Less than 70	Delay and reduce next dose to 65 mg/m ² or add filgrastim	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/m².

6. Neuropathy: Dose modification or discontinuation may be required (see BC Cancer Drug Manual).

PRECAUTIONS:

1. **Hypersensitivity:** Reactions to PACLitaxel are common. See [BC Cancer 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 epinephrine or bronchodilators if indicated▪ discontinue PACLitaxel therapy

2. **Extravasation:** PACLitaxel causes pain and tissue necrosis if extravasated. Refer to [BC Cancer Extravasation Guidelines](#).
3. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.

Call Dr. Caroline Lohrisch or tumour group delegate at 604-877-6000 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.