BC Cancer Protocol Summary for Treatment of Locally Advanced Breast Cancer using Doxorubicin and Cyclophosphamide followed by DOCEtaxel

Protocol Code	*BRLAACD*
Tumour Group	*Breast*
Contact Physician	*Dr. Stephen Chia*

ELIGIBILITY:

- locally advanced and inflammatory breast cancer in patients less than or equal to 60 years of age or fit patients greater than 60 years of age.
- For other indications, a BC Cancer "Compassionate Access Program" request must be approved.

EXCLUSIONS:

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

TESTS:

- Baseline: CBC & Diff, ALT, alkaline phosphatase, total bilirubin, GGT
- Baseline, if clinically indicated: LDH
- Before each treatment: CBC & Diff
- Prior to **cycle #5**: total bilirubin, ALT, alkaline phosphatase (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel)
- If clinically indicated: creatinine, total bilirubin, ALT, alkaline phosphatase, GGT, LDH, 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 of DOCEtaxel:
  - dexamethasone 8 mg PO bid for 3 days, starting one day prior to each DOCEtaxel administration. Patient must receive minimum of 3 doses pre-treatment.
- Additional antiemetics not usually required.
- DOCEtaxel-induced onycholysis and cutaneous toxicity of the hands may be prevented by wearing frozen gloves starting 15 minutes before DOCEtaxel infusion until 15 minutes after end of DOCEtaxel infusion; gloves should be changed after 45 minutes of wearing to ensure they remain cold during the entire DOCEtaxel infusion.

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
filgrastim (G-CSF)	5mcg/kg/day starting on Day 3, for 5 to 7 doses (adjust as needed**)	subcutaneously

*Use 250 mL for dose greater than 1000 mg

**reduce filgrastim treatment duration if ANC greater than 10 x 10^9/L or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

Repeat every 21 days x 4 cycles.

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

Drug	Dose	BC Cancer Administration Guideline
DOCEtaxel	100 mg/m^2	IV in 250 to 500 mL NS or D5W over 1 hour (see precautions #2 & 6) (use non-DEHP equipment)
filgrastim (G-CSF)	5mcg/kg/day starting on Day 3, for 5 to 7 doses (adjust as needed**)	subcutaneously

**reduce filgrastim treatment duration if ANC greater than 10 x 10^9/L or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

Repeat every 21 days x 4 cycles.

DOSE MODIFICATIONS:

1. **Hematological**

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (all drugs)
Greater than or equal to 1.0	and	Greater than or equal to 100	100%
Less than 1.0	and	Greater than or equal to 100	delay for 1 week (or longer if needed), then give 100% dose if ANC greater than 1.0 and platelets greater than or equal to 100. Increase the filgrastim treatment duration per provider discretion.
Greater than or equal to 1.0	and	Less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1.0 and platelets greater than or equal to 100
Less than 1.0	and	Less than 100	delay for 1 week (or longer if needed), then give 75% if ANC greater than 1.0 and platelets greater than or equal to 100

Febrile Neutropenia

Event	Management
1st episode	75% of previous cycle dose if Day 1 ANC greater than or equal to 1.0 and platelets greater than or equal to 100
2nd episode	50% of original cycle dose if Day 1 ANC greater than or equal to 1.0 and platelets greater than or equal to 100
3rd episode	Discontinue treatment

2. **Renal dysfunction**: Dose modification may be required for cyclophosphamide. Refer to BC Cancer Drug Manual.
3. **Hepatic dysfunction**: Dose modification required for doxorubicin and DOCEtaxel. Refer to BC Cancer Drug Manual for doxorubicin and DOCEtaxel.

PRECAUTIONS:

1. **Febrile Neutropenia** Risk of febrile neutropenia is greater than 20% without the use of filgrastim. Mandatory filgrastim reduces the risk of febrile neutropenia. Febrile neutropenia can result in patient harm, treatment delays and hospitalization. Fever or other evidence of infection must be assessed promptly and treated aggressively.
2. **Extravasation (DOXOrubicin and DOCEtaxel)**: Doxorubicin and DOCEtaxel cause pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.

3. **Cardiac Toxicity (DOXOrubicin)**: 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 BC Cancer Drug Manual.
4. **Fluid Retention (DOCEtaxel)**: Dexamethasone premedication must be given to reduce incidence and severity of fluid retention with DOCEtaxel.
5. **Hepatic Dysfunction (DOCEtaxel)**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST or ALT) may lead to increased toxicity and usually requires a dose reduction. Baseline liver enzymes are recommended before cycle 1 and then if clinically indicated (eg, repeat liver enzymes prior to each treatment if liver enzymes are elevated or there is severe toxicity such as neutropenia). Note: this information is intended to provide guidance but physicians must use their clinical judgement when making decisions regarding monitoring and dose adjustments.
6. **Hypersensitivity** reactions to DOCEtaxel are common but it is not necessary to routinely initiate the infusion slowly. If slow initiation of infusion is needed, start infusion at 30 mL/h x 5 minutes, then 60 mL/h x 5 minutes, then 120 mL/h x 5 minutes, then complete infusion at 250 mL/h (for 500 mL bag, continue 250 mL/h for 5 minutes and then complete infusion at 500 mL/h). Refer to BC Cancer SCDRUGRX protocol.
   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.
7. **Interstitial pneumonitis (DOCEtaxel)** may occur. Risk may be increased with radiation 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.

References:

1. Wolmark, N et al. The effect on primary tumor response of adding sequential Taxotere to Adriamycin and cyclophosphamide: preliminary results from NSABP Protocol B-27. [Abstract 5] Breast Cancer Res and Treat 2001;69(3):210.
2. Vandenberg T, Younus J, and Al-Hkayyat S. Febrile neutropenia rates with adjuvant docetaxel and cyclophophamide chemotherapy in early breast cancer: discrepancy between published reports and community practice – a retrospective analysis. Curr Oncol 2010 April; 17(2):2-3.
3. Soong D et al. High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. JCO 2009, 27(26): 101-2.
4. Chan A et al. Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. Supp Care Cancer 2011, 19: 497-504.
5. Jones S et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7-year follow-up of US Oncology Research Trial 9735. JCO 2009, 27(8):1177-83.