Mde theBC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Breast Cancer using Cyclophosphamide, DOXOrubicin and DOCEtaxel

Protocol Code:	*BRAJDAC*
Tumour Group:	*Breast*
Contact Physician:	*Dr. Andrew Attwell*

ELIGIBILITY:

Patient must have:

- Age less than or equal to 65 years
- Node positive early stage breast cancer (any T, N1-3)
- HER-2 negative

Patient should have:

- ECOG 0-1
- Adequate hematologic, renal and hepatic function
- Adequate cardiac function

EXCLUSIONS:

- Age greater than 65 years
- ECOG 2-4
- HER-2 positive
- Significant hepatic dysfunction
- Congestive heart failure (LVEF less than 45%) or other significant heart disease
- greater than or equal to grade 2 sensory or motor neuropathy
- Pregnancy or lactation
- Unsuitable for aggressive adjuvant chemotherapy

TESTS:

- Baseline: CBC & Diff, total bilirubin, creatinine, ALT, alkaline phosphatase, GGT
- Baseline, if clinically indicated: LDH
- Before each treatment: CBC & Diff
- If clinically indicated: total bilirubin, ALT, alkaline phosphatase, LDH, GGT, creatinine

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- Dexamethasone 8 mg PO bid for 3 days starting one day prior to DOCEtaxel. Patient must receive 3 doses prior to treatment.
- 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:

Drug	Dose	BC Cancer Administration Guideline
DOXOrubicin	50 mg/m²	IV push
cyclophosphamide	500 mg/m²	IV in NS or D5W 100 to 250 mL over 20 min to 1 hour
DOCEtaxel	75 mg/m2	IV in NS 250 to 500 mL over 1 hour (use non-DEHP equipment)
filgrastim (G-CSF)	5 mcg/kg/day Days:3 to10 (adjust as needed**)	subcutaneously

- Repeat every 21 days x 6 cycles.
- ** 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.

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. **Hepatic dysfunction:** Dose modifications required for DOXOrubicin and for DOCEtaxel. (see BC Cancer Drug Manual).
3. **Renal dysfunction:** Dose modification may be required for cyclophosphamide if creatinine clearance less than 0.3 mL/sec, i.e., less than 18 mL/minute (see BC Cancer Drug Manual).

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. **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 400 mg/m^2 to be exceeded (see BC Cancer Drug Manual).
3. **Infusion-related reactions**: Infusion-related reactions are common with DOCEtaxel 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 Infusion-Related Reactions Guidelines.
4. **Extravasation:** DOXOrubicin causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
5. **Fluid retention**: Dexamethasone premedication must be given to reduce incidence and severity of fluid retention.
6. **Hepatic Dysfunction**: DOCEtaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) 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, evolving liver metastases are suspected, or there is unexpectedly severe toxicity such as severe neutropenia).

Call Dr. Andrew Attwell or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

References:

1. Nabholtz JM, Pienkowski T, Mackey J, et al. Phase III trial comparing TAC (docetaxel, doxorubicin, cyclophosphamide) with FAC (5-flouorouracil, doxorubicin, cyclophosphamide) in the adjuvant treatment of node positive breast cancer (BC) patients: interim analysis of BCIRG 001. Proc Am Soc Clin Oncol 2002;21:36a (abstr 141).
2. Mackey JR, Paterson A, Dirix LY, et al. Final results for the phase III randomized trail comparing docetaxel (T), doxorubicin(A) and cyclophosphamide(C) to FAC as first line chemotherapy (CT) for patients (pts) with metastatic breast cancer (MBC). Proc Am Soc Clin Oncol 21:35a,2002 (abstr 137).
3. Vandenberg T, Younus J, and Al-Hkayyat S. Febrile neutropenia rates with adjuvant docetaxel and cyclophosphamide chemotherapy in early breast cancer: discrepancy between published reports and community practice – a retrospective analysis. Curr Oncol 2010;17(2):2-3.
4. Soong D, Hag R, Leung MG, et al. High rate of febrile neutropenia in patients with operable breast cancer receiving docetaxel and cyclophosphamide. J Clin Oncol 2009;27(26):101-2.
5. Chan A, FU WH, Shih V, et al. Impact of colony-stimulating factors to reduce febrile neutropenic events in breast cancer patients receiving docetaxel plus cyclophosphamide chemotherapy. Support Care Cancer 2011, 19: 497-504.
6. Jones S, Holmes FA, O'Shaughnessy J, 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. J Clin Oncol 2009;27(8):1177-83.