BC Cancer Protocol Summary for Neoadjuvant or Adjuvant Therapy for Breast Cancer Using Fluorouracil, Epirubicin, Cyclophosphamide and DOCEtaxel

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

ELIGIBILITY:

- Node positive (any T, N1-3) or high risk, node negative early stage breast cancer
- Less than or equal to 65 years of age or fit patients greater than 65 years deemed appropriate by supervising physician
- ECOG 0-1
- HER-2 negative
- Adequate renal and hepatic function
- Adequate cardiac function

EXCLUSIONS:

- ECOG 2-4
- 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, platelets, creatinine, bilirubin, ALT, Alk Phos, LDH, GGT, *DPYD* test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- Before each treatment (Day 1): CBC & diff, platelets.
- Prior to **Cycle #4**: CBC & diff, platelets, bilirubin, ALT, Alk Phos (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel).
- If clinically indicated: bilirubin, ALT, Alk Phos, creatinine, protein level, albumin, GGT, LDH, urea, MUGA scan or echocardiogram

PREMEDICATIONS:

- For the 3 cycles of epirubicin, fluorouracil and cyclophosphamide, antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- For the 3 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:

Drug	Dose	BC Cancer Administration Standard
epirubicin	100 mg/m^2 on Day 1	IV push
fluorouracil	500 mg/m^2 on Day 1	IV push
cyclophosphamide	500 mg/m^2 on Day 1	IV in 100 to 250 mL NS over 20 min to 1 hour

- Repeat every 21 days x 3 cycles
- *Followed by 3 consecutive cycles of DOCEtaxel to start **21 days after** final cycle of epirubicin, fluorouracil and cyclophosphamide*

Drug	Dose	BC Cancer Administration Guideline
DOCEtaxel	100 mg/m^2	IV in 250 to 500 mL NS over 1 hour (use non-DEHP equipment)

Repeat every 21 days x 3 cycles.

- If radiation therapy is required, it is given following completion of chemotherapy (see BC Cancer Cancer Management Manual).

DOSE MODIFICATIONS:

Fluorouracil Dosing Based on DPYD Activity Score (DPYD-AS)
Refer to "Fluorouracil and Capecitabine Dosing Based on DPYD Activity Score (DPYD-AS)" on www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual.

Doses are adjusted based on Day 1 counts (Tables 1 to 3) and previous cycle febrile neutropenia (Table 4). No dose reduction for nadir counts.

1. **Hematological**

Table 1. Cycle 1, Day 1

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose (all drugs)
greater than or equal to 1.5	and	greater than or equal to 100	100%
1.0 to less than 1.5	and	greater than or equal to 100	75%
less than 1.0	or	less than 100	ineligible for treatment

Table 2. Cycles 2 to 6, Day 1

FIRST OCCURRENCE OF LOW COUNTS when ANC less than 1.5 x10^9/L and/or platelets less than 100 x 10^9/L ***after a one week delay*** and ***no febrile neutropenia*** in a previous cycle

ANC (x 10^9/L)		Platelets (x 10^9/L)	All Chemotherapy Drugs % Dose of Previous Cycle
greater than or equal to 1.5	and	greater than or equal to 100	100%
1.0 to less than 1.5	and	greater than or equal to 100	75%
less than 1.0	or	less than 100	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 75%

Table 3. Cycles 2 to 6, Day 1

SECOND OCCURRENCE OF LOW COUNTS when ANC less than 1.5 x10^9/L and/or platelets less than 100 x 10^9/L ***after a one week delay*** and ***no febrile neutropenia*** in a previous cycle

ANC (x10^9/L)		Platelets (x 10^9/L)	All Chemotherapy Drugs % of Previous Cycle Dose	Filgrastim (G-CSF) Option
greater than or equal to 1.5	and	greater than or equal to 100	75 % of previous cycle dose	100% regimen with filgrastim 300 mcg sc daily on Days 5 to 12 (adjust as needed)
less than 1.5	and	greater than or equal to 100	Delay 1 week or until ANC greater than or equal to 1.5 - then give 75% of previous cycle dose	75% regimen with filgrastim 300 mcg sc daily on Days 5 to 12 (adjust as needed)
		less than 100	Delay 1 week or until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 75% of previous cycle dose	

Table 4. For cycles of DOCEtaxel only:

ANC (x 10^9/L)		Platelets (x10^9/L)	Dose	Dose after Febrile Neutropenia on DOCEtaxel
greater than or equal to 1.5	and	greater than 90	100%	75%
1.0 to less than 1.5	or	70 to 90	75%	Delay till recovery then 75%
less than 1.0	or	less than 70	delay	Delay till recovery then 75%

Table 5. Febrile neutropenia

Event	Dose Reduction Option	Filgrastim (G-CSF) Option
1st episode	75% of previous cycle dose if Day 1 ANC greater than or equal to 1.5 and platelets greater than or equal to 100	100% regimen with filgrastim 300 mcg sc daily on Days 5 to 12 (adjust as needed)
2nd episode	50% of original cycle dose if Day 1 ANC greater than or equal to 1.5 and platelets greater than or equal to 100	75% regimen with filgrastim 300 mcg sc daily on Days 5 to 12 (adjust as needed)
3rd episode	**No dose reduction option**	75% regimen with filgrastim 300 mcg sc daily on Days 5 to 12 (adjust as needed)

2. **Stomatitis**: For Grade 3 or 4 stomatitis (painful erythema, edema or ulcers and *cannot eat*; mucosal necrosis and/or requires enteral support; dehydration), delay until recovered then give 75% dose of Day 1 of previous cycle. Maintain dose reduction for all subsequent cycles.
2. **Hepatic Dysfunction**: Dose modification required for epirubicin if total bilirubin greater than or equal to 25 micromol/L, for fluorouracil if greater than 85 micromol/L (see BC Cancer Drug Manual) and for DOCEtaxel (Refer to 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. **Extravasation**: *Epirubicin and DOCEtaxel* causes pain and tissue necrosis if extravasated. Refer to BC Cancer Extravasation Guidelines.
2. **Febrile Neutropenia:** DOCEtaxel containing adjuvant chemotherapy for breast cancer is associated with an extreme risk of febrile neutropenia approaching 40% in real practice settings, as reported in two outcome studies from Ontario. Thus, strong consideration should be given to using prophylactic G-CSF. Febrile neutropenia rates with prophylactic GCSF are lower (5-7%) making this the safer option. Fever or other evidence of infection must be assessed promptly and treated aggressively.
3. **Cardiac Toxicity**: Clinical cardiac assessment is required prior to FEC if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF (MUGA scan or ECHO). **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil or capecitabine.** Development of cardiac symptoms including signs suggestive of ischemia or of cardiac arrhythmia is an indication to discontinue treatment. If there is development of cardiac symptoms patients should have urgent cardiac assessment. Generally re-challenge with either fluorouracil or capecitabine is not recommended as symptoms potentially have a high likelihood of recurrence which can be severe or even fatal. Seeking opinion from cardiologists and oncologists with expert knowledge about fluorouracil or capecitabine toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient's allergy profile.

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 Hypersensitivity Guidelines. 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.
8. **Possible drug interactions with fluorouracil and warfarin, phenytoin and fosphenytoin** have been reported and may occur at any time. Close monitoring is recommended (eg, for warfarin, monitor INR weekly during fluorouracil therapy and for 1 month after stopping fluorouracil).

PATIENT EDUCATION:

- For the Patient: cyclophosphamide, epirubicin, 5-fluorouracil and DOCEtaxel.

Contact 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. French Adjuvant Study 5. Benefit of a high-dose epirubicin regimen in adjuvant chemotherapy for node-positive breast cancer patients with poor prognostic factors: 5-year follow-up results of French Adjuvant Study Group 05 randomized trial. J Clin Oncol 2001;19(3):602-11.
2. Roche H, Fumoleau P, Spielmann M, et al. Five year analysis of the PACS 01 trial: 6 cycles of FEC100 versus 3 cycles of FEC100 followed by 3 cycles of docetaxel for the adjuvant treatment of node positive breast cancer. Breast Can Res Treat 2004;88(suppl 1):abstract 27.
3. Vandenberg, T, Younus, J, 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;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.