

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:

Patient must have:

- 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
- HER-2 negative

Patient should have:

- ECOG 0-1
- Adequate **hematologic** 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, creatinine, **total** bilirubin, ALT, **alkaline phosphatase**, GGT, DPYD test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- **Baseline, if clinically indicated:** LDH
- Before each treatment (Day 1): CBC & Diff
- Prior to **Cycle #4**: CBC & Diff, **total** bilirubin, ALT, **alkaline phosphatase** (see Precaution #5 for guidelines regarding hepatic dysfunction and DOCEtaxel).
- If clinically indicated: **total** bilirubin, ALT, **alkaline phosphatase**, creatinine, 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:

Cycles 1 to 3

Drug	Dose	BC Cancer Administration Guideline
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
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 $10 \times 10^9/L$ or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

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

Cycles 4 to 6

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)
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 $10 \times 10^9/L$ or intolerable bone pain. Filgrastim should not be stopped before the time of the predicted nadir from chemotherapy.

Repeat every 21 days x 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 \(DPYD-AS\)](http://www.bccancer.bc.ca/health-professionals/clinical-resources/cancer-drug-manual)” 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

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. Give filgrastim on Days 3 to 13 for remaining cycles.
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
1 st 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
2 nd 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
3 rd episode	Discontinue treatment

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:** 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.
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).

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 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.