

BCCA Protocol Summary for Adjuvant Therapy for Breast Cancer Using Fluorouracil, Epirubicin and Cyclophosphamide

Protocol Code

BRAJFEC

Tumour Group

Breast

Contact Physician

Dr. Susan Ellard

ELIGIBILITY:

- Patients less than or equal to 60 years of age or fit patients greater than 60 years of age with 1 or more axillary lymph node metastasis(es).
- High risk, lymph node-negative
- Adequate hematological parameters (ANC greater than $1.5 \times 10^9/L$ and platelets greater than $100 \times 10^9/L$)

EXCLUSIONS:

- Congestive heart failure (LVEF less than 45%) or other significant heart disease

TESTS:

- Baseline: CBC & diff, platelets, bilirubin, creatinine
- Before each treatment (Day 1): CBC & diff, platelets
- If clinically indicated: bilirubin, creatinine, MUGA scan or echocardiogram

PREMEDICATIONS:

- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)

TREATMENT:

Drug	Dose	BCCA 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 6 cycles
- Maximum cumulative epirubicin dose is 720 mg/m²
- If radiation therapy is required, it is given following completion of chemotherapy (see BCCA Cancer Management Manual).

DOSE MODIFICATIONS

Doses are adjusted based on Day 1 counts (Tables 1-2) and previous cycle febrile neutropenia (Table 3). No dose reduction for nadir counts.

1. Hematological

Table 1. FIRST OCCURRENCE OF LOW COUNTS

At the Beginning of a Cycle (Day 1):

IF ANC less than $1.5 \times 10^9/L$ and/or platelets less than $100 \times 10^9/L$, DELAY for one week

THEN after a one week delay and **no febrile neutropenia** in a previous cycle, treat as below:

ANC ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	All Chemotherapy Drugs % Dose of Previous Cycle	Filgrastim (G-CSF) Option
greater than or equal to 1.5	and	greater than or equal to 100	100%	
1 to 1.49*	and	greater than or equal to 100	75%*	100% regimen** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)
less than 1	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%	Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 100% regimen** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)

* if the ANC is greater than $1 \times 10^9/L$, 100% dose of previous cycle may be used at the discretion of the medical oncologist

**100% regimen refers to Cycle 1 doses ie. epirubicin $100 \text{ mg}/\text{m}^2$, fluorouracil $500 \text{ mg}/\text{m}^2$ and cyclophosphamide $500 \text{ mg}/\text{m}^2$

Table 2. SECOND OCCURRENCE OF LOW COUNTS

At the Beginning of a Cycle (Day 1):

IF ANC less than $1.5 \times 10^9/L$ and/or platelets less than $100 \times 10^9/L$, DELAY for one week

THEN after a one week delay and no febrile neutropenia in a previous cycle, treat as below:

ANC (x10⁹/L)	Platelets (x 10⁹/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 G-CSF 300 mcg sc daily on Days 4 to 11 (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 G-CSF 300 mcg sc daily on Days 4 to 11 (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	

**100% regimen refers to Cycle 1 doses ie. epirubicin 100 mg/m^2 , fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2

***75% regimen refers to 75% of Cycle 1 doses ie. epirubicin 75 mg/m^2 , fluorouracil 375 mg/m^2 and cyclophosphamide 375 mg/m^2

Table 3. Febrile neutropenia

Event	Dose Reduction Option	Filgrastim (G-CSF) Option
1 st 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 G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)
2 nd episode	50% of previous cycle dose if Day 1 ANC greater than or equal to 1.5 and platelets greater than or equal to 100	75% regimen*** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)
3 rd episode	No dose reduction option	Use 75% regimen*** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)

**100% regimen refers to Cycle 1 doses ie. epirubicin 100 mg/m^2 , fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2

***75% regimen refers to 75% of Cycle 1 doses ie. epirubicin 75 mg/m², fluorouracil 375 mg/m² and cyclophosphamide 375 mg/m²

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.
3. **Hepatic Dysfunction:** Dose modification required for epirubicin if total bilirubin greater than or equal to 25 micromol/L and for fluorouracil if greater than 85 micromol/L (see BCCA Cancer Drug Manual).
4. **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 BCCA Cancer Drug Manual).

PRECAUTIONS:

1. **Extravasation:** Epirubicin causes pain and tissue necrosis if extravasated. Refer to BCCA Extravasation Guidelines.
2. **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated aggressively.
3. **Cardiac Toxicity:** Clinical cardiac assessment is required prior to CEF 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. **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. Susan Ellard or tumour group delegate at (250) 712-3900 or 1-888-563-7773 with any problems or questions regarding this treatment program.

Date activated: 01 Jan 2003

Date revised: 1 Aug 2015 (number of treatment cycles clarified)

References^{1, 2}:

1. French Adjuvant Study G. 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. Del Mastro L, Venturini M, Lionetto R, et al. Accelerated-intensified cyclophosphamide, epirubicin, and fluorouracil (CEF) compared with standard CEF in metastatic breast cancer patients: results of a multicenter, randomized phase III study of the italian Gruppo Oncologico Nord-Ouest-Mammella Inter Gruppo Group. *J Clin Oncol* 2001;19(8):2213-21.