

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

Protocol Code
Tumour Group
Contact Physician

BRAJCEF
Breast
Dr. Susan Ellard

ELIGIBILITY:

- Women less than or equal to 60 years of age or fit women greater than 60 years of age with 1 or more axillary lymph node metastasis(es).
- 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 and 8): CBC & diff, platelets
- If clinically indicated: bilirubin, creatinine, MUGA scan or echocardiogram

PREMEDICATIONS:

- Antiemetic protocol for High/Moderate emetogenic chemotherapy (see protocol SCNAUSEA)

TREATMENT:

Drug	Dose	BCCA Administration Standard
Epirubicin	60 mg/m ² /day on days 1 and 8	IV push
Fluorouracil	500 mg/m ² /day on days 1 and 8	IV push
Cyclophosphamide	75 mg/m ² /day x 14 days (d1-14) (round to nearest 25 mg)	oral
Cotrimoxazole*	2 tablets bid continuously	Oral

*If allergic, substitute ciprofloxacin 500 mg po bid or norfloxacin 400 mg po bid.

- Regular antiemetics may be required on days 1-14.
- Repeat every 28 days x 6 cycles.
- 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 and Day 8 counts (Tables 1-3) and previous cycle febrile neutropenia (Table 4). No dose reduction for nadir counts.

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 (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 - 1.49*	and	greater than or equal to 100	75%*
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%

* 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

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 ($\times 10^9/L$)	and	Platelets ($\times 10^9/L$)	All Chemotherapy Drugs % of Previous Cycle Dose
greater than or equal to 1.5		greater than or equal to 100	75 % or convert to BRAJCEF-G
less than 1.5		greater than or equal to 100	Delay 1 week or until ANC greater than or equal to 1.5 then convert to BRAJCEF-G
		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 50%

Note: Following a dose reduction for Day 1 of the current cycle due to low ANC, do not attempt dose re-escalation in subsequent cycles without converting to BRAJCEF-G.

DAY 8

Table 3. Cycles 1-6, Day 8

ANC (x10 ⁹ /L)		Platelets (x 10 ⁹ /L)	All Chemotherapy Drugs % of Day 1 Dose of This Cycle	
greater than or equal to 1.5	and	greater than or equal to 100	100 %	
1.0 – 1.49	and	greater than or equal to 100	75%	
less than 1.0	and	greater than or equal to 100	Tell patient to STOP oral cyclophosphamide. Omit IV treatment.	
			1st dose reduction or delay Start next cycle on Day 22 if counts permit using 75%	2nd dose reduction or delay Start next cycle on Day 22 if counts permit using BRAJCEF-G
		less than 100	Tell patient to STOP oral cyclophosphamide. Omit IV treatment.	
			1st dose reduction or delay Start next cycle on Day 22 if counts permit using 75%	2nd dose reduction or delay Start next cycle on Day 22 if counts permit using 75%

Note: Doses modified on Day 8 due to hematological toxicity are re-escalated on Day 1 of subsequent cycles if Day 1 counts are adequate.

Table 4. 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	Convert to BRAJCEF-G using 100% regimen
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	Convert to BRAJCEF-G using 75% regimen
3 rd episode	No dose reduction option	Convert to BRAJCEF-G using 75% regimen

5. **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.
6. **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).
7. **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) and for antibiotic if less than 50 mL/minute (see product monograph).

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).
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).

PATIENT EDUCATION:

- For the Patient: CEF

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 Sep 1998

Date revised: 1 Sep 2009 (drug interaction added to Precautions)

REFERENCES:

1. Levine MN, Bramwell VH, Pritchard KI et al. Randomized trial of intensive cyclophosphamide, epirubicin, and fluorouracil chemotherapy compared with cyclophosphamide, methotrexate, and fluorouracil in premenopausal women with node-positive breast cancer. J Clin Oncol 1998;16(8):2651-8.

2. Califaretti N, Davidson M, Goss, P et al. Is there a role for G-CSF with adjuvant CEF chemotherapy for breast cancer (BC)? (abstract) Proc Am Soc Clin Oncol 1999;18:90a.
3. National Cancer Institute of Canada. Clinical Trials Group. Protocol MA.21: A phase III adjuvant trial of sequenced EC + filgrastim + epoetin alfa followed by paclitaxel versus sequenced AC followed by paclitaxel versus CEF as therapy for premenopausal women and early postmenopausal women who have had potentially curative surgery for node positive or high risk node negative breast cancer. Kingston, 02 Oct 2000.