BC Cancer 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 x 10^9/L and platelets greater than 100 x 10^9/L)

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

**TESTS:**
- Baseline: CBC & diff, platelets, bilirubin, creatinine, DPYD test (not required if previously tested, or tolerated fluorouracil or capecitabine)
- 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:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Standard</th>
</tr>
</thead>
<tbody>
<tr>
<td>epirubicin</td>
<td>100 mg/m^2 on Day 1</td>
<td>IV push</td>
</tr>
<tr>
<td>fluorouracil</td>
<td>500 mg/m^2 on Day 1</td>
<td>IV push</td>
</tr>
<tr>
<td>cyclophosphamide</td>
<td>500 mg/m^2 on Day 1</td>
<td>IV in 100 to 250 mL NS over 20 min to 1 hour</td>
</tr>
</tbody>
</table>

- Repeat every 21 days x 6 cycles
- Maximum cumulative epirubicin dose is 720 mg/m^2
- 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 1-2) 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 x 10⁹/L and/or platelets less than 100 x 10⁹/L, DELAY for one week

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

<table>
<thead>
<tr>
<th>ANC (x 10⁹/L)</th>
<th>Platelets (x 10⁹/L)</th>
<th>All Chemotherapy Drugs % Dose of Previous Cycle</th>
<th>Filgrastim (G-CSF) Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.5</td>
<td>greater than or equal to 100</td>
<td>100%</td>
<td>100% regimen** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td>1 to 1.49*</td>
<td>greater than or equal to 100</td>
<td>75%*</td>
<td></td>
</tr>
<tr>
<td>less than 1</td>
<td>less than 100</td>
<td>Delay until ANC greater than or equal to 1.5 and platelets greater than or equal to 100 then give 75%</td>
<td>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)</td>
</tr>
</tbody>
</table>

* if the ANC is greater than 1 x 10⁹/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 mg/m², fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²
Table 2. SECOND OCCURRENCE OF LOW COUNTS

At the Beginning of a Cycle (Day 1):
IF ANC less than 1.5 x10⁹/L and/or platelets less than 100 x 10⁹/L, DELAY for one week

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

<table>
<thead>
<tr>
<th>ANC (x10⁹/L)</th>
<th>Platelets (x10⁹/L)</th>
<th>All Chemotherapy Drugs</th>
<th>Filgrastim (G-CSF) Option</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater and equal to 1.5</td>
<td>greater than or equal to 100</td>
<td>75% of previous cycle dose</td>
<td>100% regimen** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td>less than 1.5 and greater than or equal to 100</td>
<td>Delay 1 week or until ANC greater than or equal to 1.5 - then give 75% of previous cycle dose</td>
<td>75% regimen*** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)</td>
<td></td>
</tr>
<tr>
<td>less than 100</td>
<td>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</td>
<td>75% regimen*** with G-CSF 300 mcg sc daily on Days 4 to 11 (adjust as needed)</td>
<td></td>
</tr>
</tbody>
</table>

**100% regimen refers to Cycle 1 doses ie. epirubicin 100 mg/m², fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²

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

Table 3. Febrile neutropenia

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

**100% regimen refers to Cycle 1 doses ie. epirubicin 100 mg/m², fluorouracil 500 mg/m² and cyclophosphamide 500 mg/m²

***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 BC 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 BC Cancer Drug Manual).

**PRECAUTIONS:**

1. **Extravasation**: Epirubicin causes pain and tissue necrosis if extravasated. Refer to BC Cancer 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.

**References**
