5-Fluorouracil, epiRUBicin 50 and Cyclophosphamidе (FEC 50) Therapy

INDICATIONS FOR USE:

<table>
<thead>
<tr>
<th>INDICATION</th>
<th>ICD10</th>
<th>Regimen Code</th>
<th>Reimbursement Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metastatic breast carcinoma</td>
<td>C50</td>
<td>00269a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

Fluorouracil, epiRUBicin and cyclophosphamide are administered once every 21 days until disease progression, maximum dose of epirubicin is reached or unacceptable toxicity occurs.

<table>
<thead>
<tr>
<th>Admin. Order</th>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
<th>Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>EpiRUBicin</td>
<td>50mg/m²</td>
<td>IV Bolus</td>
<td>Via the tubing of a free-running intravenous saline infusion over a period of up to 30min.</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>5-Fluorouracil</td>
<td>500mg/m²</td>
<td>IV Bolus</td>
<td>N/A</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Cyclophosphamide</td>
<td>500mg/m²</td>
<td>IV</td>
<td>250ml 0.9% NaCl over 30min</td>
<td>Every 21 days</td>
</tr>
</tbody>
</table>

Lifetime cumulative dose for epiRUBicin is 900mg/m².

In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below and to the age of the patient.

* Cyclophosphamide may also be administered as an IV bolus over 5-10mins

Radiation is contraindicated in combination with chemotherapy because of toxicity.

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Adequate haematological, renal and liver status.

EXCLUSIONS:

- Hypersensitivity to fluorouracil, epiRUBicin, cyclophosphamide or any of the excipients.
- Uncontrolled high blood pressure, unstable angina, symptomatic congestive heart failure, myocardial infarction within the preceding 6 months, serious uncontrolled cardiac dysrhythmia.
- Patients previously treated with maximum cumulative doses of epiRUBicin or any other anthracycline.
- Pregnancy or lactation.
Fluorouracil (5-FU) should not be given to patients who are known to be homozygotic for dihydropyrimidine dehydrogenase (DPD) or in patients with a known complete absence of DPD activity.

**PRESCRIPTIVE AUTHORITY:**
The treatment plan must be initiated by a Consultant Medical Oncologist.

**TESTS:**

**Baseline tests:**
- FBC, renal and liver profile.
- ECG
- MUGA scan or echocardiogram if clinically indicated or > 65 years.

**Regular tests:**
- FBC, renal and liver profile prior to each cycle.
- MUGA scan or echocardiogram if clinically indicated.

**Disease monitoring:**
Disease monitoring should be in line with the patient’s treatment plan and any other test/s as directed by the supervising Consultant.

**DOSE MODIFICATIONS:**
- Any dose modification should be discussed with a Consultant.
- Doses are adjusted based on Day 1 counts (table 1) and previous cycle febrile neutropenia (table 2).
- No dose reduction for nadir counts.
- G-CSF prophylaxis (using standard or pegylated form) may be added up front at the discretion of the prescribing consultant.

**Haematological:**

**First and Second occurrence of low counts:** At the beginning of a cycle (Day 1):
- If ANC < 1.5 x10⁹/L and/or platelets < 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 1).
Table 1: First and Second Occurrence of Low Counts

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose (Day 1)</th>
<th>G-CSF option</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1.5 and ≥ 100</td>
<td>1st occurrence</td>
<td>100%</td>
<td>100% regimen ** with G-CSF on Days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td></td>
<td>2nd occurrence</td>
<td>75% of previous cycle dose</td>
<td>75% regimen *** with G-CSF daily on Days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td>1 to 1.49 and ≥ 100</td>
<td>1st occurrence</td>
<td>75%*</td>
<td>Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 100% regimen with G-CSF daily on days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td></td>
<td>2nd occurrence</td>
<td>Delay 1 week or until ANC ≥ 1.5, then give 75% of previous cycle dose</td>
<td>Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 100% regimen with G-CSF daily on days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td>&lt;1 or &lt;100</td>
<td>1st occurrence</td>
<td>Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 75%</td>
<td>Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 75% regimen with G-CSF daily on Days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td>&lt;100</td>
<td>2nd occurrence</td>
<td>Delay 1 week or until ANC ≥ 1.5 and platelets ≥ 100 then give 75% of previous cycle dose</td>
<td>Delay until ANC ≥ 1.5 and platelets ≥ 100 then give 75% regimen with G-CSF daily on Days 4 to 11 (adjust as needed)</td>
</tr>
</tbody>
</table>

* If the ANC > 1 x 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 i.e. epirubicin 50 mg/m^2, fluorouracil 500 mg/m^2 and cyclophosphamide 500 mg/m^2

***75% regimen refers to 75% of Cycle 1 doses

Table 2: Febrile neutropenia

<table>
<thead>
<tr>
<th>Event</th>
<th>Dose Reduction Option</th>
<th>G-CSF option</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st episode</td>
<td>75% of previous cycle dose if Day 1 ANC ≥ 1.5 and platelets ≥ 100</td>
<td>100% regimen ** with G-CSF 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 ≥ 1.5 and platelets ≥ 100</td>
<td>75% regimen *** with G-CSF daily on Days 4 to 11 (adjust as needed)</td>
</tr>
<tr>
<td>3rd episode</td>
<td>No dose reduction option</td>
<td>75% regimen *** with G-CSF daily on Days 4 to 11 (adjust as needed)</td>
</tr>
</tbody>
</table>

**100% regimen refers to Cycle 1 doses i.e. 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
Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<tr>
<td>S-Fluorouracil</td>
<td>Consider dose reduction in severe impairment only</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</td>
</tr>
<tr>
<td>epiRUBicin</td>
<td>Dose reduction may need to be considered where CrCl &lt;10ml/min. Clinical decision</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>24-51</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51-85</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>CrCl (ml/min)</td>
<td>Dose</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>100%</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75%</td>
</tr>
<tr>
<td></td>
<td>&lt;10</td>
<td>50%</td>
</tr>
</tbody>
</table>

Management of adverse events:

Table 4: Dose modifications based on Adverse Events

<table>
<thead>
<tr>
<th>Adverse reactions</th>
<th>Recommended dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade ≥ 3 Stomatitis</td>
<td>Delay treatment until recovered then give 75% dose of Day 1 of previous cycle. Maintain dose reduction for all subsequent cycles</td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

**EMETOGENIC POTENTIAL:** High (Refer to local policy).

**PREMEDICATIONS:** Not usually required

**OTHER SUPPORTIVE CARE:**

Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide.
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Extravasation**: EpiRUBicin causes pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
- **Cardiac Toxicity**: Clinical cardiac assessment is required prior to epiRUBicin if cardiac function is equivocal and recommended at any time if clinically indicated with a formal evaluation of LVEF. **Myocardial ischemia and angina occurs rarely in patients receiving fluorouracil.** 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 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 toxicity is strongly advised under these circumstances. The toxicity should also be noted in the patient’s allergy profile.
- **DPD deficiency**: This may result in severe and unexpected toxicity to fluorouracil – stomatitis, diarrhea, neutropenia, neurotoxicity – secondary to reduced drug metabolism. This deficiency is thought to be present in about 3% of the population. Fluorouracil should be permanently discontinued in patients exhibiting exaggerated or prolonged neutropenia, mucositis, and diarrhea.

**DRUG INTERACTIONS:**

- Fluorouracil significantly reduces the metabolism of warfarin. INR and signs of bleeding should be monitored regularly and dose of warfarin adjusted as required.
- Fluorouracil (5-FU) is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5-FU-metabolising enzyme dihydropyrimidine dehydrogenase (DPD).
- Current drug interaction databases should be consulted for more information.

**ATC CODE:**

- 5-Fluorouracil L01BC02
- EpiRUBicin L01DB03
- Cyclophosphamide L01AA01

**REFERENCES:**

3. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; NortLondon Cancer Network. Available at http://londoncancer.org/media/65600/renal-impairment-dosage-adjustment-for-

https://www.hpра.ie/image/uploaded/swdocuments/Licence_PA22766-003-001_29052019163017.pdf


7. Fluorouracil 50 mg/ml Solution for Injection or Infusion SmPC HPRA. Last updated 10/05/2019. Accessed Nov 2019. Available at;

8. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V1 2018. Available at:

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient