EpiRUBicin 75 + Cyclophosphamide (EC75) Therapy-21 day

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>00263a</td>
<td>Hospital</td>
</tr>
</tbody>
</table>

*If the reimbursement status is not defined*, the indication has yet to be assessed through the formal HSE reimbursement process.

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.

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

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

<table>
<thead>
<tr>
<th>Order of Admin</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>75mg/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>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>IV infusion*</td>
<td>250ml 0.9% sodium chloride over 30min</td>
<td>Every 21 days</td>
</tr>
</tbody>
</table>

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

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.

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

EXCLUSIONS:
- Hypersensitivity to 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 and lactation.
PRESCRIPTIVE AUTHORITY:
The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:
Baseline tests:
- FBC, renal and liver profile.
- ECG
- MUGA or echocardiogram if clinically indicated

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

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

Haematological:

<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>Dose (Day 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 and</td>
<td>&gt; 100</td>
<td>100%</td>
</tr>
<tr>
<td>&lt; 1.0 or</td>
<td>&lt; 100</td>
<td>Delay for 1 week</td>
</tr>
</tbody>
</table>

Consider decreasing to 75% if an episode of febrile neutropenia occurs with the prior cycle of treatment.

Renal and Hepatic Impairment:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Renal Impairment</th>
<th>Hepatic Impairment</th>
</tr>
</thead>
<tbody>
<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>≥ 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>

May consider the use of G-CSF in adjuvant therapy after an episode of febrile neutropenia or neutropenic sepsis.

NCCP Protocol: EC (75-600) Therapy-21 day
Tumour Group: Breast
NCCP Protocol Code: 00263
Published: 29/04/2015
Review: 19/06/2021
Version number: 5

The information contained in this document is a statement of consensus of NCCP and ISMO or IHS professionals regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult these documents is expected to use independent medical judgement in the context of individual clinical circumstances to determine any patient’s care or treatment. Use of these documents is the responsibility of the prescribing clinician and is subject to HSE’s terms of use available at http://www.hse.ie/egg/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPchemoprotocols
SUPPORTIVE CARE:
EMETOGENIC POTENTIAL: High (Refer to local policy)
PREMEDICATIONS: None 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.

DRUG INTERACTIONS:
- CYP3A inhibitors decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers may also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Current drug interaction databases should be consulted for more information.

ATC CODE:
EpiRUBicin L01DB03
Cyclophosphamide L01AA01

REFERENCES:
Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects. Risk factors for developing anthracycline-induced cardiotoxicity include:

- high cumulative dose, previous therapy with other anthracyclines or anthracenediones
- 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.