NCCP Chemotherapy Regimen

epiRUBicin, Oxaliplatin and 5-Fluorouracil (EOF) -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>Locally advanced or metastatic gastric carcinoma</td>
<td>C16</td>
<td>00429a</td>
<td>Hospital</td>
</tr>
<tr>
<td>Locally advanced or metastatic oesophageal carcinoma</td>
<td>C15</td>
<td>00429b</td>
<td>Hospital</td>
</tr>
<tr>
<td>Locally advanced or metastatic gastroesophageal carcinoma</td>
<td>C16</td>
<td>00429c</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.

epiRUBicin and oxaliplatin are administered on day 1 and 5-fluorouracil is administered continuously throughout the 21 day cycle until disease progression or unacceptable toxicity develops.

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

<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>&quot;epiRUBicin&quot;</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>Oxaliplatin</td>
<td>130mg/m²</td>
<td>IV</td>
<td>500ml glucose 5% over 2hours*</td>
<td>Every 21 days</td>
</tr>
<tr>
<td>3</td>
<td>1, 8, and 15</td>
<td>&quot;5-Fluorouracil&quot;</td>
<td>200mg/m²/day</td>
<td>Continuous IV infusion over 7 days</td>
<td>Infusor pump</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.

*Increase infusion rate time to 4 – 6 hours in case of laryngopharyngeal dyshaesethia reaction.

Oxaliplatin is incompatible with sodium chloride 0.9%.

*Total 7 day dose of 5-fluorouracil = 1400mg/m²

ELIGIBILITY:

- Indications as above
- ECOG status 0-2
- Expected survival > 2 months
- Adequate haematological, renal and liver status

NCCP Regimen: EOF Therapy
Published: 28/07/2017
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Version number: 3

Tumour Group: Gastrointestinal
NCCP Regimen Code: 00429
ISM0 Contributor: Prof Maccon Keane

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/eng/Disclaimer

This information is valid only on the day of printing, for any updates please check www.hse.ie/NCCPChemoRegimens
EXCLUSIONS:

- Hypersensitivity to epiRUBicin, oxaliplatin, 5-fluorouracil or any of the excipients
- Patients previously treated with maximum cumulative doses of epiRUBicin or any other anthracycline
- Patients with current or previously significant cardiac disease; LVEF < 50%, uncontrolled congestive heart disease, unstable angina or myocardial infarction within the last 6 months
- Pregnancy and lactation
- Severe leucopenia, neutropenia or thrombocytopenia
- Severe renal impairment (creatinine clearance below 30 ml/min at baseline)
- Severe hepatic impairment
- Fluorouracil should not be given to patients 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, liver and renal profile.
- MUGA scan or echocardiogram.

Regular tests:
- FBC, liver and renal 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

### Haematological:

<table>
<thead>
<tr>
<th>ANC x 10^9/L</th>
<th>Platelets x 10^9/L</th>
<th>Dose modification</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥1.0</td>
<td>and</td>
<td>100%</td>
</tr>
<tr>
<td>0.5-0.9</td>
<td>or</td>
<td>Delay treatment until counts recover. Reduce epiRUBicin next cycle by 25% and oxaliplatin to 100mg/m^2</td>
</tr>
<tr>
<td>&lt; 0.5</td>
<td>or</td>
<td>Delay treatment until counts recover. Reduce epiRUBicin next cycle by 50% and oxaliplatin to 100mg/m^2</td>
</tr>
<tr>
<td>&lt;25</td>
<td></td>
<td>Delay treatment until platelets recover to &gt;75. Omit epiRUBicin from subsequent cycles and reduce oxaliplatin to 100mg/m^2</td>
</tr>
</tbody>
</table>

Note: Reduce epiRUBicin by 25% and oxaliplatin to 100mg/m^2 if > 2 week delay due to neutropenia.
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 or 2-5 x ULN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>51-85 or &gt;5 x ULN</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>Moderate renal impairment 100% Monitor renal function. Dose adjust according to toxicity</td>
<td>Little information available. Probably no dose reduction necessary Clinical decision.</td>
</tr>
<tr>
<td>5-Fluorouracil</td>
<td>Consider dose reduction in severe renal impairment only</td>
<td>Bilirubin (micromol/L)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&lt;85 or &lt;180</td>
</tr>
<tr>
<td></td>
<td></td>
<td>&gt;85 or &gt;180</td>
</tr>
</tbody>
</table>

Oxaliplatin induced neuropathy:

<table>
<thead>
<tr>
<th>Toxicity Grade</th>
<th>Dose Modification of oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1</td>
<td>100%</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Reduce dose to 100mg/m²</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Reduce dose to 100mg/m²</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Discontinue oxaliplatin</td>
</tr>
<tr>
<td>Grade 4</td>
<td>Discontinue oxaliplatin</td>
</tr>
</tbody>
</table>
5-Fluorouracil

Table 4: Dose modification table for 5-Fluorouracil based on adverse events.

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>Dose modification of 5-Fluorouracil</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hand-Foot syndrome</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>Skin changes or dermatitis without pain e.g. erythema, peeling</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Skin changes with pain not interfering with function</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Skin changes with pain, interfering with function</td>
</tr>
<tr>
<td><strong>Stomatitis</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>Painless ulcers, erythema or mild soreness</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Painful erythema, edema, or ulcers but can eat</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>As above, but cannot eat, mucosal necrosis, requires parenteral support.</td>
</tr>
<tr>
<td><strong>Diarrhoea</strong></td>
<td></td>
</tr>
<tr>
<td>Grade 1</td>
<td>Increase of 2-3 stools/day or nocturnal stools; or moderate increase in loose watery colostomy output</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Increase of 4-6 stools/day, or nocturnal stools or moderate increase in loose watery colostomy output</td>
</tr>
<tr>
<td>Grade 3 or 4</td>
<td>Increase of greater than 7 stools/day or grossly bloody diarrhea, or incontinence, malabsorption; or severe increase in loose watery colostomy output requiring parenteral support</td>
</tr>
</tbody>
</table>

**SUPPORTIVE CARE:**

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

**PREMEDICATIONS:** Not usually required unless the patient has had a previous hypersensitivity.

**OTHER SUPPORTIVE CARE:**
Medication may be required for management of diarrhoea, e.g. loperamide (4mg at first onset followed by 2mg after each loose stool (max 16 mg /day) or see local policy.
ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:
The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full
details.

- **Diarrhoea and dehydration:** This may be dose limiting. Patients with severe diarrhoea should be carefully
  monitored and given fluid and electrolyte replacement if they become dehydrated.

- **Neutropenia:** Fever or other evidence of infection must be assessed promptly and treated appropriately
  in line with the National Sepsis Guidelines.

**epiRUBicin:**

- **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.

- **Extravasation:** EpiRUBicin causes pain and tissue necrosis if extravasated (Refer to local policy).

**Oxaliplatin:**

- **Platinum Hypersensitivity:** Special surveillance should be ensured for patients with a history of allergic
  manifestations to other products containing platinum. In case of anaphylactic manifestations the infusion
  should be interrupted immediately and an appropriate symptomatic treatment started. Re-
  administration of oxaliplatin to such patients is contraindicated.

- **Laryngopharyngeal dysesthesia:** An acute syndrome of pharyngolaryngeal dysesthesia occurs in 1-2% of
  patients and is characterised by subjective sensations of dysphagia or dyspnoea/feeling of suffocation,
  without any objective evidence of respiratory distress (no cyanosis or hypoxia) or of laryngospasm or
  bronchospasm. Symptoms are often precipitated by exposure to cold. Although antihistamines and
  bronchodilators have been administered in such cases, the symptoms are rapidly reversible even in the
  absence of treatment. Prolongation of the infusion helps to reduce the incidence of this syndrome.

- **Gastrointestinal toxicity:** It manifests as nausea and vomiting and warrants prophylactic and/or
  therapeutic anti-emetic therapy. Dehydration, paralytic ileus, intestinal obstruction, hypokalemia,
  metabolic acidosis and renal impairment may be caused by severe diarrhoea/emesis particularly when
  combining oxaliplatin with 5Fluorouracil.

- **Extravasation:** Oxaliplatin causes irritation if extravasated (Refer to local policy).

- **Venous occlusive disease:** A rare but serious complications that has been reported in patients (0.02%)
  receiving oxaliplatin in combination with fluorouracil. This condition can lead to hepatomegaly,
  splenomegaly, portal hypertension and/or esophageal varices. Patients should be instructed to report
  any jaundice, ascites or hematemesis immediately.

- **Haemolytic Uremic Syndrome (HUS):** Oxaliplatin therapy should be interrupted if HUS is suspected:
  hematocrit is less than 25%, platelets less than 100,000 and creatinine greater than or equal to 135
  micromol/L. If HUS is confirmed, oxaliplatin should be permanently discontinued.

**5-Fluorouracil:**

- **Myocardial ischaemia and angina:** Cardiotoxicity is a serious complication during treatment with
  fluorouracil. Patients, especially those with a prior history of cardiac disease or other risk factors, treated
  with fluorouracil, should be carefully monitored during therapy.

- **Dihydropyrimidine dehydrogenase (DPD) deficiency:** Rare, life-threatening toxicities such as stomatitis,
  mucositis, neutropenia, neurotoxicity and diarrhoea have been reported following administration of
  fluoropyrimidines (e.g. fluorouracil and capecitabine). Severe unexplained toxicities require investigation
  prior to continuing with treatment.
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.
- Concurrent administration of fluorouracil and phenytoin may result in increased serum levels of phenytoin.
- Fluorouracil is contraindicated in combination with brivudin, sorivudin and analogues as these are potent inhibitors of the 5’-Fluorouracil metabolising enzyme dihydropyrimidine dehydrogenase (DPD). Caution is advised when oxaliplatin treatment is co-administered with other medicinal products known to cause QT interval prolongation. In case of combination with such medicinal products, the QT interval should be closely monitored.
- Current drug interaction databases should be consulted for more information.

ATC CODE:

- EpiRUBicin L01DB03
- Oxaliplatin L01XA03
- 5-FU L01BC02

REFERENCES:


<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>28/06/2017</td>
<td></td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>2</td>
<td>04/09/2019</td>
<td>Standardisation of treatment table and renal and hepatic modification table. Update of adverse events and drugs interactions.</td>
<td>Prof Maccon Keane</td>
</tr>
<tr>
<td>3</td>
<td>09/10/2019</td>
<td>Update of exclusion</td>
<td>Prof Maccon Keane</td>
</tr>
</tbody>
</table>

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.
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.