Chemotherapy Protocol

BREAST CANCER

CYCLOPHOSPHAMIDE-EPIRUBICIN-PACLITAXEL

Regimen

- Breast Cancer – Cyclophosphamide-Epirubicin-Paclitaxel

Indication

- Neoadjuvant / adjuvant therapy of early breast cancer
- WHO Performance status 0, 1

Toxicity

<table>
<thead>
<tr>
<th>Drug</th>
<th>Adverse Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Dysuria, haemorrhagic cystitis, taste disturbances</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Cardio-toxicity, urinary discolouration (red)</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia and back pain on administration</td>
</tr>
</tbody>
</table>

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Regimen

- FBC, U&E’s and LFT’s prior to each cycle.
- Ensure adequate cardiac function before starting treatment with epirubicin. Baseline LVEF should be measured, particularly in patients with a history of cardiac problems or in the elderly
- Blood pressure and pulse to be monitored half hourly during the paclitaxel infusion

Dose Modifications

The dose modifications listed are for haematological, liver and renal function only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.
Please discuss all dose reductions / delays with the relevant consultant before prescribing if appropriate. The approach may be different depending on the clinical circumstances. The following is a general guide only.

**Haematological**

Prior to prescribing the following treatment criteria must be met on day one of treatment.

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Eligible Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophils</td>
<td>equal to or more than $1\times 10^9$/L</td>
</tr>
<tr>
<td>Platelets</td>
<td>equal to or more than $100\times 10^9$/L</td>
</tr>
</tbody>
</table>

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL

If counts on day one are below these criteria for neutrophils and platelets then delay treatment for seven days. Treatment should only be re-started when these levels are reached. Treatment may be resumed at the original dose or reduce the original dose of cyclophosphamide, epirubicin or paclitaxel to 80% of the original dose where a NCI-CTC grade 3 or above haematological event has occurred. If a second episode of neutropenia and / or thrombocytopenia occurs, despite dose reduction, or the time to reach the eligible level is longer than seven days consider changing or stopping therapy.

**Kidney Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Creatinine Clearance (ml/min)</th>
<th>Dose (% of original dose)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>more than 20</td>
<td>100</td>
</tr>
<tr>
<td></td>
<td>10-20</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Less than 10</td>
<td>50</td>
</tr>
<tr>
<td>Epirubicin</td>
<td></td>
<td>Dose reduce in severe impairment only</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td></td>
<td>No dose reductions necessary</td>
</tr>
</tbody>
</table>

**Liver Impairment**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>Dose reduction may not be necessary</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>Bilirubin (umol/L)</td>
</tr>
<tr>
<td></td>
<td>24-51</td>
</tr>
<tr>
<td></td>
<td>51-85</td>
</tr>
<tr>
<td></td>
<td>85 or greater</td>
</tr>
<tr>
<td></td>
<td>If AST 2-4 x ULN or bilirubin 21-51μmol/L give 50% dose , if the AST greater than 4 x ULN or bilirubin greater than 51μmol/L then give 25% dose</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Bilirubin (umol/L)</td>
</tr>
<tr>
<td></td>
<td>less than 26</td>
</tr>
<tr>
<td></td>
<td>27-51</td>
</tr>
<tr>
<td></td>
<td>greater than 51</td>
</tr>
<tr>
<td></td>
<td>If bilirubin less than 1.25 x ULN and transaminase less than 10 x ULN, dose at 175 mg/m²</td>
</tr>
</tbody>
</table>
Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

Epirubicin

Discontinue epirubicin if cardiac failure develops.

Paclitaxel

NCI-CTC grade 2 peripheral neuropathy withhold paclitaxel only until the neuropathy recovers to NCI-CTC grade 1 then dose reduce to 75% of the original dose. Where the peripheral neuropathy is NCI-CTC grade 3 again withhold the paclitaxel until it resolves to NCI-CTC grade 1 and then reduce the dose of paclitaxel to 50% of the original dose. Paclitaxel should be discontinued if the neuropathy does not resolve to NCI-CTC grade 1.

Regimen

21 day cycle for 4 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclophosphamide</td>
<td>600mg/m²</td>
<td>1</td>
<td>Intravenous bolus</td>
</tr>
<tr>
<td>Epirubicin</td>
<td>90mg/m²</td>
<td>1</td>
<td>Intravenous bolus</td>
</tr>
</tbody>
</table>

Followed by

21 day cycle for 4 cycles

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Days</th>
<th>Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>175mg/m²</td>
<td>1</td>
<td>Intravenous infusion in 500ml sodium chloride over 180 minutes</td>
</tr>
</tbody>
</table>

Dose Information

- Cyclophosphamide will be dose banded in accordance with the national dose bands (20mg/mL)
- Epirubicin will be dose banded in accordance with the national dose bands (2mg/ml)
- The maximum lifetime cumulative dose of epirubicin is 900mg/m².
• Paclitaxel will be dose banded in accordance with the national dose bands (6mg/ml)

**Administration Information**

• Hypersensitivity reactions tend to occur with the first or second infusion of paclitaxel. Paclitaxel infusions should be interrupted for minor symptoms such as flushing or localised rashes. If these resolve promptly (within 5 minutes) the infusion may be restarted at a lower rate with intensive monitoring. Immediately discontinue the infusion for severe reactions which include profound hypotension, bronchospasm and generalised erythema.

• Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter.

**Extravasation**

• Cyclophosphamide - neutral
• Epirubicin – vesicant
• Paclitaxel – vesicant

**Additional Therapy**

• Antiemetics

15-30 minutes prior to chemotherapy with **cyclophosphamide and epirubicin**

- dexamethasone 8mg oral or intravenous
- ondansetron 8mg oral or intravenous

As take home medication;

- dexamethasone 4mg twice a day oral for 3 days
- metoclopramide 10mg three times a day when required oral
- ondansetron 8mg twice a day oral for 3 days

15-30 minutes prior to chemotherapy with **paclitaxel**

- metoclopramide 10mg oral or intravenous

As take home medication

- metoclopramide 10mg three times a day when required oral

• Premedication to reduce of risk of paclitaxel hypersensitivity reaction
30 minutes prior to chemotherapy with paclitaxel

- chlorphenamine 10mg intravenous
- dexamethasone 20mg intravenous
- H₂ antagonist according to local formulary choice and availability

- Mouthwashes according to local or national policy on the treatment of mucositis

- Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

References
REGIMEN SUMMARY

Cyclophosphamide-Epirubicin-Paclitaxel

Cyclophosphamide-Epirubicin

Cycle 1, 2, 3, 4

1. Dexamethasone 8mg oral or intravenous
2. Ondansetron 8mg oral or intravenous
3. Epirubicin 90mg/m² intravenous bolus over 10 minutes.
4. Cyclophosphamide 600mg/m² intravenous bolus over 10 minutes.

Take Home Medicines

5. Dexamethasone 4mg twice a day oral for 3 days starting on day two of the cycle
6. Metoclopramide 10mg three times a day when required oral
7. Ondansetron 8mg twice a day oral for three days starting on the evening of day one of treatment

Paclitaxel

Cycle 5, 6, 7, 8

1. Chlorphenamine 10mg intravenous
2. Dexamethasone 20mg intravenous
3. H₂ antagonist according to local formulary choice and availability

   Administration Instructions:
   Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy:
   - ranitidine 50mg intravenous once only
   - famotidine 20mg oral once only
   - nizatidine 150mg oral once only
   - ranitidine 150mg oral once only

If there is no stock of these products due to national shortages treatment may proceed without the H₂ antagonist provided there is no instruction in the ARIA journal indication the patient must have H₂ antagonist treatment.

All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. Many Trusts do not administer an H₂ antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

4. Metoclopramide 10mg oral or intravenous
5. Paclitaxel 175mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes

Take Home Medicines

6. Metoclopramide 10mg three times a day when required oral
## DOCUMENT CONTROL

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Amendment</th>
<th>Written By</th>
<th>Approved By</th>
</tr>
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<tbody>
<tr>
<td>1.3</td>
<td>Nov 2023</td>
<td>Typographical error, doxorubicin changed to epirubicin on page 1 under regimen header.</td>
<td>Eleanor Taylor Oncology Pharmacist</td>
<td>Tom Hurst Pharmacy Technician</td>
</tr>
<tr>
<td>1.2</td>
<td>Nov 2020</td>
<td>Update of premedication due to shortage of IV ranitidine. IV ranitidine changed to H₂ antagonist according to local formulary choice and availability. Dose banding updated. Coding removed.</td>
<td>Donna Kimber Pharmacy Technician</td>
<td>Rebecca Wills Pharmacist</td>
</tr>
<tr>
<td>1</td>
<td>Dec 2011</td>
<td>None</td>
<td>Dr Debbie Wright Pharmacist</td>
<td>Dr Ellen Copson Consultant Medical Oncologist</td>
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</tbody>
</table>

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

- Hampshire Hospitals NHS Foundation Trust
- NHS Isle of Wight
- Portsmouth Hospitals NHS Trust
- Salisbury Hospital NHS Foundation Trust
- University Hospital Southampton NHS Foundation Trust
- Western Sussex Hospitals NHS Foundation Trust
All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.