Chemotherapy Protocol

BREAST CANCER

CYCLOPHOSPHAMIDE-EPIRUBICIN-PACLITAXEL-ACCELERATED

Regimen

- Breast Cancer – Cyclophosphamide-Epirubicin-Paclitaxel (accelerated)

Indication

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

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis, taste disturbances
Epirubicin	Cardio-toxicity, urinary discolouration (red)
Paclitaxel	Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia and back pain on administration

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 doxorubicin. 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 1 of SACT.

Criteria	Eligible Level
Neutrophils	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

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

If counts on day 1 are below these criteria for neutrophils and platelets then delay treatment for 7 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 occurs, despite dose reduction, or the time to reach the eligible level is longer than 7 days consider changing or stopping therapy.

Kidney Impairment

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

Liver Impairment

Drug	Recommendation	
Cyclophosphamide	If bilirubin greater than 30umol/L or AST/ALT greater than 2xULN clinical decision. Evidence that exposure to active metabolites may not be increased, suggesting dose reduction may not benecessary. There may be decreased efficacy in severe hepatic impairment.	
Epirubicin	**Bilirubin (umol/L)**	**Dose (% of original)**
	24-51	50
	52-85	25
	85 or greater	Contra-indicated
	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	
Paclitaxel	less than 26 27-51 greater than 51	135mg/m² 75mg/m² 50mg/m²
	If bilirubin less than 1.25 x ULN and transaminase less than 10xULN, dose at 175 mg/m²	

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

14 day cycle for 4 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	600mg/m^2	1	Intravenous bolus
Epirubicin	90mg/m^2	1	Intravenous bolus

Followed by

14 day cycle for 4 cycles

Drug	Dose	Days	Administration
Paclitaxel	175mg/m^2	1	Intravenous infusion in 500ml sodium chloride over 180 minutes

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/m^2.

- 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

- Growth Factors according to local formulary choice.

  - filgrastim or bioequivalent 30million units once a day subcutaneous for 5 days starting on day 3 of the cycle.
  - lenograstim or bioequivalent 33.6million units once a day subcutaneous for 5 days starting on day 3 of the cycle.

- pegfilgrastim, lipegfilgrastim or bioequivalent 6mg once a day subcutaneous on day 2 of the cycle

- Premedication to reduce of risk of paclitaxel hypersensitivity reaction

  30 minutes prior to chemotherapy with paclitaxel

  - chlorphenamine 10mg intravenous
  - dexamethasone 20mg intravenous
  - H_2 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 H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

References

1. Medac GmbH (2012). Epirubicin hydrochloride 2mg/ml solution for injection summary of product characteristics. Available from: www.medicines.org.uk (accessed 04/08/2022).

2. Sandoz Limited (2021). Cyclophosphamide 1000mg powder for solution for injection or infusion summary of product characteristics. Available from: www.medicines.org.uk (accessed 04/08/2022).

3. Hospira UK Ltd (2020). Paclitaxel 6mg/ml concentrate for solution for infusion summary of product characteristics. Available from: www.medicines.org.uk (accessed 04/08/2022).

4. Early Breast Cancer Trialists' Collaborative group (2019). Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient-level meta-analysis of 37298 women with early breast cancer in 26 randomised trials. The Lancet. 393 (10179); 1440-1452.

REGIMEN SUMMARY

Cyclophosphamide-Epirubicin-Paclitaxel (accelerated)

Cycle 1, 2, 3, 4

1. Dexamethasone 8mg oral or intravenous
   Administration instructions:
   Administer 15-30 minutes prior to chemotherapy
   This may be given as dexamethasone (dose) IV stat, or equivalent dose, if required.

2. Ondansetron 8mg oral or intravenous
   Administration instructions:
   Administer 15-30 minutes prior to chemotherapy. This may be given as ondansetron 8mg IV stat if required.

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
   Administration Instructions:
   Take with or after food.

6. Metoclopramide 10mg three times a day when required oral
   Administration instructions:
   Please supply 5 days or an original pack if appropriate.

7. Ondansetron 8mg twice a day oral for three days starting on the evening of day one of treatment

8. Growth Factors according to local formulary choice.
   Administration instructions:

   - filgrastim or bioequivalent 30million units once a day subcutaneous for 5 days starting on day 3 of the cycle.
   - lenograstim or bioequivalent 33.6million units once a day subcutaneous for 5 days starting on day 3 of the cycle
   - pegfilgrastim, lipegfilgrastim or bioequivalent 6mg once a day subcutaneous on day 2 of the cycle for 1 day

Cycle 5, 6, 7, 8

9. Chlorphenamine 10mg intravenous

10. Dexamethasone 20mg intravenous

11. H_2 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 H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 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 H_2 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.

12. Metoclopramide 10mg oral or intravenous

Administration instruction:
Administer 15-30 minutes prior to chemotherapy
This may be given as metoclopramide 10mg IV stat if required.

13. Paclitaxel 175mg/m² intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes

Administration instruction
Paclitaxel should be administered using a PVC free administration set containing an in-line 0.22micron filter.

Take Home Medicines

14.Metoclopramide 10mg three times a day when required oral

Administration instructions:
Please supply 5 days or an original pack if appropriate.

15.Growth Factors according to local formulary choice.

Administration instructions:
- filgrastim or bioequivalent 30million units once a day subcutaneous for 5 days starting on day 3 of the cycle.
- lenograstim or bioequivalent 33.6million units once a day subcutaneous for 5 days starting on day 3 of the cycle.
- pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day 2 of the cycle for 1 day

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1	August 2022	None	Alexandra Pritchard Pharmacist	Dr Marcus Remer Consultant

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.