Chemotherapy Protocol

BREAST CANCER

CYCLOPHOSPHAMIDE-DOCETAXEL-EPIRUBICIN (100)- FLUOROURACIL

($FE_{100}CT$)

Regimen

- Breast Cancer – Cyclophosphamide-Docetaxel-Epirubicin (100)-Fluorouracil ($FE_{100}CT$)

Indication

- Neo-adjuvant / adjuvant therapy of breast cancer
- WHO Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis, taste disturbances
Docetaxel	Hypersensitivity, fluid retention, neuropathy, joint pains, nail changes, fatigue
Epirubicin	Cardio-toxicity, urinary discolouration (red)
Fluorouracil	Diarrhoea, stomatitis

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. Baseline LVEF should be measured, particularly in patients with a history of cardiac problems or in the elderly.
- Patients with complete or partial dihydropyrimidine dehydrogenase (DPD) deficiency are at increased risk of severe and fatal toxicity during treatment with fluorouracil. All patients should be tested for DPD deficiency before initiation (cycle 1) to minimise the risk of these reactions

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 treatment.

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

In the adjuvant / neo-adjuvant setting always check with the relevant consultant before delaying or reducing the dose in response to a toxicity.

For the FEC arm of treatment. If counts on day one are below these criteria for neutrophil and/or platelets then delay treatment for seven days. Treatment should only be started when these levels are reached. On subsequent cycles, if the counts are below these levels on day one then delay treatment until these levels are reached and / or consider reducing the dose of epirubicin to 75% of the original dose. The dose intensity of cyclophosphamide and fluorouracil may be maintained. If a second episode of neutropenia / thrombocytopenia occurs or the time to reach the eligible level is longer than seven days consider changing treatment. If patients experience febrile neutropenia or treatment delay due to neutrophil less than $0.5x10^9$/L or platelets less than $50x10^9$/L for more than a week, then reduce the dose to 75% of the original dose. If neutropenia or thrombocytopenia recurs, the dosage should be either further reduce to 50% of the original dose or stop treatment.
For docetaxel the following table applies.

Toxicity	Grade (NCI-CTC)	Previous Docetaxel Dose		
		100mg/m^2	**75mg/m^2**	**60mg/m^2**
Neutrophil	1	100mg/m^2	75mg/m^2	60mg/m^2
	2	Delay until grade 1 then 100mg/m^2	Delay until grade 1 then 75mg/m^2	Delay until grade 1 then 60mg/m^2
	3	Delay until grade 1 then 100mg/m^2	Delay until grade 1 then 75mg/m^2	Delay until grade 1 then 60mg/m^2
	4	Delay until grade 1 then 75mg/m^2	Delay until grade 1 then 60mg/m^2	Stop
Febrile Neutropenia	3	Delay until grade 1 then 75mg/m^2	Delay until grade 1 then 60mg/m^2	Stop
	4	Delay until grade 1 then 75mg/m^2	Delay until grade 1 then 60mg/m^2	Stop
Platelets	Greater than or equal to 100x10^9/L	100mg/m^2	75mg/m^2	60mg/m^2
	Less than 100x10^9/L	Delay until greater than or equal to 100x10^9/L then 75mg/m^2	Delay until greater than or equal to 100x10^9/L then 60mg/m^2	Stop

Kidney Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide	more than 20	100
	10-20	75
	Less than 10	50
Docetaxel	No dose adjustment necessary	
Epirubicin	Dose reduce in severe impairment only	
Fluorouracil	Consider dose reduction in severe renal impairment only	

Liver Impairment

Drug	Recommendation	
Cyclophosphamide	Dose reduction may not be necessary	
	Bilirubin (umol/L)	**Dose (% of original)**
Epirubicin	24-51	50
	51-85	25
	85 or greater	Contra-indicated
	If the AST 2-4xULN or the bilirubin is 21-51µmol/L give 50% of the dose, then if then AST is greater than 4xULN or the bilirubin is greater than 51µmol/L then give 25% dose	

Drug	Bilirubin (µmol/L)		AST/ALT (units)		Alk Phos (units)	Dose (% of original dose)
Docetaxel	N/A		1.5xULN or greater	and	2.5xULN or greater	Give 75%
	Greater than ULN	and/or	3.5xULN or greater	and	6xULN or greater	Not Recommended

Drug	Bilirubin µmol/L		AST/ALT units	Dose (%of original dose)
Fluorouracil	Less than 85		Less than 180	100%
	More than 85	or	More than 180	CI
	In moderate hepatic impairment reduce the initial dose by one third. In severe hepatic impairment reduce initial dose by one half. These doses may be increased if no toxicity occurs			

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.

Docetaxel

Peripheral neuropathy at NCI-CTC grade 3 should result in a dose reduction from 100mg/m^2 to 75mg/m^2. If the NCI-CTC grade 3 neuropathy occurred at doses lower than 100mg/m^2 or a NCI-CTC grade 4 toxicity develops CONSIDER stopping treatment.

Excessive tearing / lacrimation are related to cumulative docetaxel doses and occur after a median of 400mg/m². Symptomatic treatment with hypromellose 0.3% eye drops four times a day may help. However, if the ocular irritation continues reduce the docetaxel dose to 80% of the original dose in the first instance.

Delay the docetaxel where a NCI-CTC grade 3 cutaneous toxicity is present on day one of the cycle until it resolves to NCI-CTC grade 1 or below. The subsequent doses of docetaxel should be reduced to from 100mg/m^2 to 75mg/m^2 or from 75mg/m^2 to 60mg/m^2. If it occurs with a dose of 60mg/m2 or if there is no recovery after two weeks, docetaxel treatment should be stopped. Where a NCI-CTC grade 3 cutaneous toxicity occurs between cycles with recovery by day one then reduce the docetaxel dose as described. Docetaxel should be stopped in response to a NCI-CTC grade 4 cutaneous toxicity.

Epirubicin

Discontinue epirubicin if cardiac failure develops.

Regimen

The complete course of $FE_{100}C$ is always administered first and is followed by docetaxel.

$FE_{100}C$ 21 day cycle for 3 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	500mg/m^2	1	Intravenous bolus
Epirubicin	100mg/m^2	1	Intravenous bolus
Fluorouracil	500mg/m^2	1	Intravenous bolus

Docetaxel 21 day cycle for 3 cycles

Docetaxel is highly myelosuppressive and in those with poor bone marrow reserves, (for example due to extensive prior treatment, bone metastasis or extensive skeletal radiation), consider a starting dose of 75mg/m^2 with a view to increase to 100mg/m^2 if well tolerated.

Drug	Dose	Days	Administration
Docetaxel	100mg/m^2	1	Intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Dose Information

- Cyclophosphamide will be dose banded in accordance with the national dose bands (20mg/ml PM)
- Docetaxel 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 PM)
- The maximum lifetime cumulative dose of epirubicin is 900mg/m^2.

- Fluorouracil will be dose banded in accordance with the national dose bands (25mg/ml PM)

Administration Information

- Hypersensitivity reactions tend to occur with the first or second infusion of docetaxel. Docetaxel infusion should not be interrupted for minor symptoms such as flushing or localised rashes. Immediately discontinue the infusion for severe reactions which include profound hypotension, bronchospasm and generalised erythema.

Extravasation

- Cyclophosphamide – neutral
- Docetaxel – exfoliant
- Epirubicin – vesicant
- Fluorouracil - inflammitant

Additional Therapy

- **$FE_{100}C$** antiemetics day 1

  15-30 minutes prior to chemotherapy;

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

As take home medication

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

Growth factor according to local formulary choice. For example;

- filgrastim or bioequivalent 300microgram once a day subcutaneous for five days starting on day five of the cycle
- lenograstim or bioequivalent 263microgram once a day subcutaneous for five days starting on day five of the cycle
- pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two of the cycle

Docetaxel

15-30 minutes before chemotherapy

- metoclopramide 10mg oral or intravenous

As take home medication

- metoclopramide 10mg three times a day when required oral

- To prevent fluid retention and hypersensitivity reactions prescribe dexamethasone 8mg twice a day oral for three days starting 24 hours before docetaxel administration. On the occasions where individuals attend for treatment and have forgotten to take the dexamethasone pre-medication administer dexamethasone 20mg as a once only dose intravenous bolus. The patient should be counselled to take the dexamethsone 8mg twice a day the following day.

- Growth factor according to local formulary choice. For example;

  - filgrastim or bioequivalent 300microgram once a day subcutaneous for seven days starting on day three of the cycle
  - lenograstim or bioequivalent 263microgram once a day subcutaneous for seven days starting on day three of the cycle
  - pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two of the cycle

- 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.Roche H, Fumoleau P, Spielmann M et al. Sequential adjuvant Epirubicin based and Docetaxel chemotherapy for node positive breast cancer patients: the FNCLCC PACS 01 trial. J Clin Oncol 2006; 24 (36): 5664-5671.

REGIMEN SUMMARY

Cyclophosphamide-Docetaxel-Epirubicin (100)-Fluorouracil ($FE_{100}CT$)

$FE_{100}C$

Cycle 1, 2 Day 1

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Epirubicin 100mg/m² intravenous bolus over 10 minutes

4. Fluorouracil 500mg/m² intravenous bolus over 10 minutes

5. Cyclophosphamide 500mg/m² intravenous bolus over 10 minutes

Take Home Medicines

6. Dexamethasone 4mg twice a day for 3 days oral starting on day two of the cycle

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

8. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

9. Growth factor according to local formulary choice. For example;

- filgrastim or bioequivalent 300microgram once a day subcutaneous for five days starting on day five of the cycle
- lenograstim or bioequivalent 263microgram once a day subcutaneous for five days starting on day five of the cycle
- pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two

$FE_{100}C$

Cycle 3 Day 1

1. Dexamethasone 8mg oral or intravenous

2. Ondansetron 8mg oral or intravenous

3. Epirubicin 100mg/m² intravenous bolus over 10 minutes

4. Fluorouracil 500mg/m² intravenous bolus over 10 minutes

5. Cyclophosphamide 500mg/m² intravenous bolus over 10 minutes

Take Home Medicines

6. Dexamethasone 4mg twice a day for 3 days oral starting on day two of the cycle

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

8. Ondansetron 8mg twice a day for 3 days oral starting on the evening of day one of treatment

9. Growth factor according to local formulary choice. For example;

- filgrastim or bioequivalent 300microgram once a day subcutaneous for five days starting on day five of the cycle
- lenograstim or bioequivalent 263microgram once a day subcutaneous for five days starting on day five of the cycle
- pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two

10. Dexamethasone 8mg twice a day oral for three days starting the day before the docetaxel infusion

Docetaxel

Cycle 4, 5 Day Minus 1

1. Dexamethasone 8mg twice a day oral*

Day 1

2. Dexamethasone 8mg twice a day oral (from TTO)*

3. Metoclopramide 10mg oral or intravenous

4. Docetaxel 100mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Take Home Medicines

5. Dexamethasone 8mg twice daily oral for 3 days starting the day before the docetaxel infusion

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

7. Growth factor according to local formulary choice. For example;

- filgrastim or bioequivalent 300microgram once a day subcutaneous for seven days starting on day three of the cycle
- lenograstim or bioequivalent 263microgram once a day subcutaneous for seven days starting on day three of the cycle
- pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two

Cycle 6 Day Minus 1

1. Dexamethasone 8mg twice a day oral*

Day 1

2. Dexamethasone 8mg twice a day oral (from TTO)*

3. Metoclopramide 10mg oral or intravenous

4. Docetaxel 100mg/m² intravenous infusion in 250ml sodium chloride 0.9% over 60 minutes

Take Home Medicines

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

6. Dexamethasone 8mg twice a day oral for the day after chemotherapy*

7. Growth factor according to local formulary choice. For example;

- filgrastim or bioequivalent 300microgram once a day subcutaneous for seven days starting on day three of the cycle
- lenograstim or bioequivalent 263microgram once a day subcutaneous for seven days starting on day three of the cycle
- pegfilgrastim or bioequivalent 6mg once a day subcutaneous on day two

* In Aria Planner the dexamethasone 8mg twice daily will appear on days 1, 2, 3 of treatment. This is the supply for the next cycle. The administration instructions reflect this. On the last cycle no dexamethasone will appear for prescribing.

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Nov 2020	Updated monitoring with DPD testing Dose banding updated Coding removed	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1.1	August 2014	Header changed Toxicities removed Adverse effects tabulated ≥ removed and written in full Dose modification tabulated Hepatic impairment updated Regimen tabulated Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed OPCS codes updated Dexamethasone TTO clarified Ondansetron TTO clarified Disclaimer added	Donna Kimber Pharmacy Technician	Dr Debbie Wright Pharmacist
1	Nov 2011	None	Anna Bunch Pharmacist Dr Debbie Wright Pharmacist	Dr Ellen Copson Consultant Medical Oncologist Dr Caroline Archer Consultant Medical Oncologist

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 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.