Chemotherapy Protocol

BREAST CANCER

CYCLOPHOSPHAMIDE–FLUOROURACIL-METHOTREXATE

(CMF IV)

Regimen

- Breast Cancer – Cyclophosphamide IV-Fluorouracil-Methotrexate (CMF IV)

Indication

- Adjuvant treatment of early breast cancer
- WHO Performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Cyclophosphamide	Dysuria, haemorrhagic cystitis, taste disturbances
Fluorouracil	Diarrhoea, stomatitis
Methotrexate	Stomatitis, conjunctivitis, renal toxicity

The presence of a third fluid compartment e.g. ascities or renal failure may delay methotrexate clearance hence increase toxicity.

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.
- 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
Neutrophil	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 one are below these criteria for the neutrophils and/or 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, methotrexate and fluorouracil to 80% of the original dose depending on clinical circumstances. If a second episode of neutropenia and / or thrombocytopenia occurs or the time to reach the eligible level is longer than 7 days consider stopping or changing treatment or growth factor support as per local guidelines.

Day 8 treatment is seldom delayed for low blood counts.

Kidney Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Cyclophosphamide	More than 20	100%
	10-20	75
	Less than 10	50 Consider mesna
Fluorouracil	Consider dose adjustments in severe renal impairment	
Methotrexate	More than 80	100%
	60	65%
	45	50%
	Less than 30	CI

Liver Impairment

Drug	Bilirubin µmol/L		AST/ALT units	Dose (%of original dose)
Cyclophosphamide	Dose reduction may not be necessary			
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			
Methotrexate	Less than 50	and	Less than 180	100%
	51-85	or	More than 180	75%
	More than 85			CI

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.

Regimen

28 day cycle for 6 cycles

Drug	Dose	Days	Administration
Cyclophosphamide	600mg/m^2	1,8	Intravenous bolus
Fluorouracil	600mg/m^2	1,8	Intravenous bolus
Methotrexate	40mg/m^2	1,8	Intravenous bolus

Dose Information

- Cyclophosphamide will be dose banded in accordance with the national dose bands (20mg/ml PM)
- Fluorouracil will be dose banded in accordance with the national dose bands (25mg/ml PM)
- Methotrexate will be dose banded in accordance with the national dose bands (25mg/ml)

Extravasation

- Cyclophosphamide - neutral
- Fluorouracil - inflammitant
- Methotrexate - inflammitant

Additional Therapy

- Antiemetics

  15-30 minutes prior to chemotherapy on days 1 and 8;

  - dexamethasone 8mg oral or equivalent intravenous dose
  - metoclopramide 10mg oral or intravenous

  As take home medication:

  - dexamethasone 4mg once a day for 3 days oral
  - metoclopramide 10mg three times a day when required oral (may not be required on day 8)

- Folinic acid 15mg six hourly for 6 doses oral starting 24 hours after methotrexate administration.
- 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.Coskun U, Gunel N, Onuk E et al. Effect of different neoadjuvant chemotherapy regimens on locally advanced breast cancer. Neoplasma 2003; 50 (3): 210-216.
2.Bonnadonna G, Brusamoline E, Valagussa P et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976; 294: 405-410.

REGIMEN SUMMARY

Cyclophosphamide IV-Fluorouracil-Methotrexate (CMF IV)

Day One

1. Dexamethasone 8mg oral or equivalent intravenous dose

2. Metoclopramide 10mg oral or intravenous

3. Fluorouracil 600mg/m² intravenous bolus over 10 minutes

4. Methotrexate 40mg/m² intravenous bolus over 10 minutes.

5. Cyclophosphamide 600mg/m² intravenous bolus over 10 minutes.

Take Home Medicines

6. Dexamethasone 4mg once a day for 3 days oral starting on the day after chemotherapy

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

8. Folinic acid 15mg six hourly for six doses oral starting 24 hours after methotrexate administration oral

Day Eight

1. Dexamethasone 8mg oral or equivalent intravenous dose

2. Metoclopramide 10mg oral or intravenous

3. Fluorouracil 600mg/m² intravenous bolus over 10 minutes

4. Methotrexate 40mg/m² intravenous bolus over 10 minutes.

5. Cyclophosphamide 600mg/m² intravenous bolus over 10 minutes.

Take Home Medicines

6. Dexamethasone 4mg once a day for 3 days oral starting on the day after chemotherapy

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

8. Folinic acid 15mg six hourly for six doses oral starting 24 hours after methotrexate administration oral

*Only dispense if required

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 Regimen tabulated Metoclopramide dose changed to 10mg Bolus removed from intravenous bolus throughout text Mucositis recommendation changed OPCS code updated Dexamethasone TTO clarified Disclaimer added	Donna Kimber Pharmacy Technician	Dr Debbie Wright Pharmacist
1	June 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.