FEC-T (Fluorouracil, Epirubicin and Cyclophosphamide and Docetaxel)

Indication
Adjuvant or neo-adjuvant treatment for high risk early and locally advanced breast cancer.

(NICE CG80)

ICD-10 codes
Codes with a prefix C50

Regimen details
Cycles 1-3

Day	Drug	Dose	Route
1	Epirubicin	*100mg/m^2	IV bolus
1	Fluorouracil	500mg/m^2	IV bolus
1	Cyclophosphamide	500mg/m^2	IV bolus

*lower doses of 60mg/m^2 or 75mg/m^2 may be used for patients with significant co-morbidity

Cycles 4-6

Day	Drug	Dose	Route
1	Docetaxel	100mg/m^2	IV infusion

Cycle frequency
21 days

Number of cycles
Maximum of 6 cycles (3 x FEC100 followed by 3 x docetaxel)

Administration
Epirubicin, fluorouracil and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions.

Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of docetaxel and therefore facilities for the treatment of hypotension and bronchospasm must be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve re-started at a slower infusion rate. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of docetaxel and appropriate therapy.

Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel.

Pre-medication

FEC cycles: none usually required

Docetaxel cycles: Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to chemotherapy. (Note: Patients must receive 3 doses of dexamethasone prior to treatment).
In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

Emetogenicity

FEC cycles: moderate - high emetic potential

Docetaxel cycles: moderate emetic potential

Additional supportive medication

Primary GCSF prophylaxis as per local policy
Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered.

Extravasation

Epirubicin is a vesicant (Group 5)
Fluorouracil is an inflammatant (Group 5)
Cyclophosphamide is neutral (Group 1)
Docetaxel is an exfollient

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days

ECHO or MUGA if significant cardiac history or previous anthracycline treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 20 mL/min
Bilirubin	≤ 1.0 ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- **Haematological toxicity**

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery.

If febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week consider reducing doses of all drugs to 80% for future cycles.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
<10	50%

There is no data available on the use of epirubicin or fluorouracil in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).
Docetaxel: consider dose reduction if CrCl <10mL/min (consultant decision).

- **Hepatic impairment**

FEC cycles:

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Epirubicin dose**	**Fluorouracil dose**	**Cyclophosphamide dose**
< 1.5	and	≤ 2.0	and	≤ 2.5	100%	100%	100%
1.5 - < 3	or	> 2.0 -3.5	or	> 2.5 - <5	50%	100%	100%*
≥3 - 5	or	> 3.5	or	5-10	25%	Consider dose reduction (discuss with consultant)	Consider dose reduction (discuss with consultant)
> 5			or	> 10	Omit	Omit	Contraindicated

*Cyclophosphamide is not recommended if bilirubin > 1.5 x ULN or AST/ALT > 3 x ULN (consultant decision).

Docetaxel cycles:

AST/ALT (x ULN)		**Alkaline phosphatase*** (x ULN)	**Docetaxel dose**
≤ 1.5	and	< 2.5	100%
> 1.5	or	≥ 2.5- 6	75%
> 3.5	or	≥ 6	Discuss with consultant

*unless due to bone metastases only.
If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

- **Other toxicities**

For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ grade 1 and reduce dose of fluorouracil and epirubicin to 80% dose.

Any other grade 3 or 4 toxicity- discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Secondary malignancy
Myelosuppression
Infusion related reactions
Anaphylaxis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia

- **Other side effects**

Fluid retention
Red urine (for 24 hours post epirubicin)
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Phenytoin: requires close monitoring if using concurrently.

Co-trimoxazole/trimethoprim: enhances antifolate effect. Avoid if possible, if essential, monitor FBC regularly.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose.

Docetaxel:
CYP3A4 Enzyme inducers/inhibitors: in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise docetaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels.

Additional comments

Cardiotoxicity has been associated with anthracyclines and fluoropyramidine therapy, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Dihydropyrimidine dehydrogenase (DPD) deficiency can result in severe toxicity secondary to reduced fluorouracil metabolism – avoid use in patients with known DPD deficiency.

Epirubicin has a life time maximum cumulative dose of 900mg/m^2

References

- Bonneterre, J., et al. JSC. 2005. 23 (12) 2686-2693
- Summary of Product Characteristics Epirubicin (Hospira) accessed 9 July 2014 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide accessed 9 July 2014 via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 9 July 2014 via www.medicines.org.uk
- Summary of Product Characteristics Docetaxel (Sanofi Aventis) accessed 9 July 2014 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. Clinical Guideline 80 – Early breast cancer accessed 9 July 2014 via www.nice.org.uk

Written/reviewed by: Dr M Beresford (Consultant Oncologist, Royal United Hospital, Bath)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

Date: 14 January 2015