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

Indication

An option for the neo-adjuvant treatment of triple negative invasive breast cancer.

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 4-7

Day	Drug	Dose	Route
1	Docetaxel	75mg/m^2	IV infusion
1	Carboplatin	AUC6*	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) an EDTA should be performed. If using an EDTA consider dosing at AUC 5 and if using Cockcroft and Gault consider dosing at AUC 6.
CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

Maximum of 7 cycles (3 x FEC 100 followed by 4 x docetaxel + carboplatin)

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.

Carboplatin is administered in 250-500mL glucose 5% over 30-60 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 + carboplatin 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 + carboplatin cycles: moderate - high 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 2)
Cyclophosphamide is neutral (Group 1)
Docetaxel is an exfoliant (Group 4)
Carboplatin is an irritant (Group 3)

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.
Baseline EDTA if suspected or significant renal dysfunction.

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)	> 30mL/min (and <10% change in CrCl from previous cycle)
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.

FEC cycles:
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.

Docetaxel & Carboplatin cycles:
Following an episode of febrile neutropenia reduce docetaxel to 60mg/m^2 and carboplatin dose by 1 x AUC for all future doses.

If thrombocytopenia (nadir platelets ≤ 50 x 10^9/L) reduce docetaxel to 60mg/m^2 and carboplatin dose by 1 x AUC for all future doses.

- **Renal impairment**

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

Epirubicin and fluorouracil: There is no data available on use in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).

Docetaxel: There is no data available on the use of docetaxel in severe renal impairment, consider dose reduction

if CrCl <10mL/min (consultant decision).

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	EDTA then 100% dose
< 20	Omit

If CrCl falls by more than 10% from the previous cycle then consider a dose reduction.

- **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 + carboplatin 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

If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. If bilirubin ≥ 3 x ULN and/or transaminases ≥ 5 x ULN discuss with consultant.

- **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.

Toxicity	**Definition**	**Docetaxel dose**
Peripheral neuropathy	Grade 2	75%
	Grade 3 or 4	Discuss with consultant
Diarrhoea	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%
Stomatitis	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%

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
Interstitial pneumonitis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity

- **Frequently occurring side effects**

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

- **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
Azathioprine: increased risk of hepatotoxicity
Clozapine: increased risk of agranulocytosis – avoid concomitant use
CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
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.

Carboplatin:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin
Yellow fever vaccine: contraindicated

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

- Summary of Product Characteristics Epirubicin (Accord) accessed 13 October 2020 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 13 October 2020 via www.medicines.org.uk
- Summary of Product Characteristics Fluorouracil (Hospira) accessed 13 October 2020 via www.medicines.org.uk
- Summary of Product Characteristics Docetaxel (Seacross) accessed 13 October 2020 via www.medicines.org.uk
- Summary of Product Characteristics Carboplatin (Accord) accessed 13 October 2020 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. Clinical Guideline 101 – Early and locally advanced breast cancer: diagnosis and management accessed 13 October 2020 via www.nice.org.uk
- Poggio, et al. 2018. Platinum-based neoadjuvant chemotherapy in triple-negative breast cancer: a systematic review and meta-analysis. Annals of oncology . 2018 29:1497-1508.

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Date: December 2020