

EC-T (Epirubicin and Cyclophosphamide and Docetaxel) - Breast**Indication**

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

(NICE NG101)

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	Cyclophosphamide	500mg/m ²	IV bolus

*lower doses of 60mg/m² or 75mg/m² 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 EC followed by 3 x docetaxel)

Administration

Epirubicin 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

EC 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

EC cycles: moderate - high emetic potential

Docetaxel cycles: moderate emetic potential

Additional supportive medication

Primary GCSF prophylaxis as per local policy

Antiemetics as per local policy

Mouthwashes as per local policy

H₂ antagonist or proton-pump inhibitor if required

Loperamide if required.

Scalp cooling may be offered.

Extravasation

Epirubicin is a vesicant (Group 5)

Cyclophosphamide is neutral (Group 1)

Docetaxel is an exfoliant (Group 4)

Investigations – pre first cycle

Investigation	Validity period
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
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)	≥ 20ml/min
AST/ALT	≤ 1.5 x ULN
Bilirubin	≤ ULN
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- Haematological toxicity**

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

If febrile neutropenia or neutrophils $< 0.5 \times 10^9/L$ 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%

Epirubicin: There is no data available in severe renal impairment. Consider dose reduction if CrCl $<10\text{mL}/\text{min}$ (consultant decision).

Docetaxel: consider dose reduction if CrCl $<10\text{mL}/\text{min}$ (consultant decision).

- Hepatic impairment**

EC cycles:

Bilirubin (x ULN)		AST/ALT (x ULN)		Alkaline phosphatase (xULN)	Epirubicin dose
< 1.5	and	≤ 2.0	and	≤ 2.5	100%
1.5 - < 3	or	> 2.0 -3.5	or	> 2.5 - <5	50%
$\geq 3 - 5$	or	> 3.5	or	5-10	25%
> 5			or	> 10	Omit

Cyclophosphamide is not recommended if bilirubin $> 1.5 \times \text{ULN}$ or AST/ALT $> 3 \times \text{ULN}$ (consultant decision).

Docetaxel cycles:

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

*unless due to bone metastases only.

If bilirubin $> 1.0 \times \text{ULN}$ withhold dose (or consultant decision to treat)

- Other toxicities**

For grade 3 or 4 mucositis/stomatitis – delay until resolved to \leq grade 1 and reduce dose of 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	1 st occurrence – 75%
		2 nd occurrence – 60%
Stomatitis	Grade 3 or 4	1 st occurrence – 75%
		2 nd 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**

Myelosuppression
Anaphylaxis
Interstitial pneumonitis
Teratogenicity
Infertility/Early menopause
Cardiotoxicity
Other primary cancer

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
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.

Additional comments

Cardiotoxicity has been associated with anthracycline 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.

Epirubicin has a lifetime maximum cumulative dose of 900mg/m²

References

- Bonnetterre, J., et al. J Clin Oncol 2005. 23 (12) 2686-2693
- Summary of Product Characteristics Epirubicin (Accord) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Docetaxel (Accord) accessed 28th April 2022 via www.medicines.org.uk
- National Institute for Health and Care Excellence. NICE Guideline 101 – Early breast cancer accessed 28th April 2022 via www.nice.org.uk

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