

Dose dense EC-Paclitaxel (Epirubicin and Cyclophosphamide and Paclitaxel)

Indication

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

ICD-10 codes

Codes with a prefix C50

Regimen details

Cycles 1-4 EC

Day	Drug	Dose	Route
1	Epirubicin	90mg/m ²	IV bolus
1	Cyclophosphamide	600mg/m ²	IV bolus

Cycles 5-8 Paclitaxel

Day	Drug	Dose	Route
1	Paclitaxel*	175mg/m ²	IV infusion

*Paclitaxel may also be administered weekly at 80mg/m² for 8-12 weeks

Cycle frequency

14 days with GCSF support.

Number of cycles

Maximum of 8 cycles (4 x EC followed by 4 x paclitaxel)

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.

Paclitaxel is administered as an IV infusion in 500mL PVC free sodium chloride 0.9% via a 0.22 in line filter over 3 hours.

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 paclitaxel 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 paclitaxel and appropriate therapy.

Pre-medication

EC cycles: none usually required

Paclitaxel cycles: A corticosteroid, antihistamine and H₂ antagonist should be given 30 minutes prior to the infusion.

For example:

Dexamethasone 16-20mg IV (8mg if paclitaxel administered weekly)

Chlorphenamine 10mg IV

Ranitidine 50mg IV or Cimetidine 300mg IV

Emetogenicity

EC cycles: moderate - high emetic potential

Paclitaxel cycles: moderate emetic potential

Additional supportive medication

GCSF must be prescribed for 2 weekly cycles as per local policy

Mouthwashes as per local policy

H₂ antagonist or proton-pump inhibitor if required

Loperamide if required.

Extravasation

Epirubicin and paclitaxel are vesicant (Group 5)

Cyclophosphamide is neutral (Group 1)

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	48 hours
U+E (including creatinine)	96 hours
LFTs	96 hours

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	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
Creatinine Clearance (CrCl)	$> 20 \text{ mL/min}$
Bilirubin	$\leq 1.0 \text{ ULN}$
AST/ALT	$\leq 2.0 \times \text{ULN}$ (see below for further information)
Alkaline Phosphatase	$\leq 2.5 \times \text{ULN}$

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 more than one delay in EC change to 3 weekly cycle. For paclitaxel consider changing to weekly dosing.

If febrile neutropenia despite GCSF 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%

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

Paclitaxel: no dose modifications recommended.

- Hepatic impairment**

EC cycles:

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

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

Paclitaxel cycles:

Bilirubin (x ULN)		AST/ALT (x ULN)	Paclitaxel dose
<ULN	and	<5	100%
1-1.5	and		135mg/m ²
1.5-2.5	and		75mg/m ²
2.5-4	and		50mg/m ²
> 4	or	≥ 5	Not recommended (consultant decision)

- Other toxicities**

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

For grade 2 neuropathy – reduce paclitaxel to 80% dose. If persists consider further dose reduction.

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.

Paclitaxel:

Clozapine: increased risk of agranulocytosis

Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Additional comments

Epirubicin has a life time maximum cumulative dose of 900mg/m²

References

- Summary of Product Characteristics Epirubicin (Hospira) accessed 9 July 2020 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide (Sandoz) accessed 9 July 2020 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Sanofi Aventis) accessed 9 July 2020 via www.medicines.org.uk
- Del Maestro, L., et al. Fluorouracil and Dose Dense Chemotherapy in adjuvant treatment of patients with early stage breast cancer. Lancet 2015. 385. 1863-1872
- EBCTCG. Increasing the dose intensity of chemotherapy by more frequent administration or sequential scheduling: a patient level meta-analysis of 37 298 women with early breast cancer in 26 randomised trials, Lancet 2019. 393. 1440-52

Written/reviewed by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust)

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

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

Date: July 2020
