Dose dense EC-paclitaxel

Indication
Adjuvant treatment for breast cancer

Regimen details

Cycles 1-4 EC

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

Cycles 5-8 Paclitaxel

Drug	Dose	Route
Paclitaxel	175mg/m^2	IV infusion

Cycle frequency
Given every 2 weeks

Number of cycles
See above

Administration
Epirubicin and cyclophosphamide are administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%

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.

Paclitaxel must be administered via a 0.2micrometer in-line filter

Pre-medication
Paclitaxel:
Dexamethasone 20mg IV
Chlorphenamine 10mg IV
Ranitidine 50mg IV (or other available H_2 antagonist)

Emetogenicity
EC – high
Paclitaxel – low

Additional supportive medication
Pegfilgrastim 6mg subcutaneously 24 hours after each cycle

Extravasation

Epirubicin and paclitaxel are vesicant
Cyclophosphamide is neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days

ECHO or MUGA if significant cardiac history or previous anthracycline treatment

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST)

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophil count	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	> 20 mL/min
Bilirubin	≤ 1.0 x ULN
AST	≤ 2.0 x ULN (see notes below)
Alkaline phosphatase	≤ 2.5 x ULN

Dose modifications

Haematological toxicity

If neutrophils <1.0 x 109 /L and/or platelets <100 x 109/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 x 109/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 <10ml/min

Paclitaxel: no dose modifications recommended

Hepatic Impairment

EC:

Bilirubin (x ULN)		AST/ALT (x ULN)		Alkaline phosphatase (x ULN)	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%*
≥ 3 – 5	Or	> 3.5	And	5 – 10	25%	Consider dose reduction
> 5			Or	> 10	Omit	Contraindicated

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

Other Toxicities
For grade 3 or 4 mucositis/stomatitis – delay until resolved to ≤ 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

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.

Enzyme inducers/inducers:
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/m^2

References

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

134O - Dose-dense adjuvant chemotherapy in early-stage breast cancer patients: End-of-study results from a randomised, phase III trial of the Gruppo Italiano Mammella (GIM) Annals of Oncology (2022) 33 (suppl_7): S55-S84. 10.1016/annonc/annonc1038

THIS PROTOCOL HAS BEEN DIRECTED BY DR EATON, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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