EC (Epirubicin & Cyclophosphamide) / Carboplatin + Weekly Paclitaxel (Breast)

Indication
Neoadjuvant or adjuvant treatment of invasive early-stage and locally advanced triple negative breast cancer.

ICD-10 codes
Codes with a prefix C50

Regimen details

Cycles 1-3 (EC)

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

Cycles 4-7 (carboplatin + weekly paclitaxel)

Day	Drug	Dose	Route
1	Carboplatin	AUC5*	IV infusion
1, 8, 15	Paclitaxel	80mg/m^2	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
Measured GFR (such as 24-hour urine or 51Cr-EDTA) is preferred whenever feasible, particularly in circumstances of co-morbidity that could affect renal function such as dehydration or extremes of weight. Alternatively the Cockcroft and Gault method can also be used to estimate a patient's CrCl.
CrCl should be capped at 125mL/min.

Cycle frequency
Cycle 1-3: EC every 21 days
Cycle 4-7: carboplatin + paclitaxel weekly every 21 days

Number of cycles
Maximum of 7 cycles (3 x EC followed by 4 x carboplatin + weekly paclitaxel)
Note: scheduling can also be reversed to give the carboplatin and weekly paclitaxel cycles prior to the EC cycles.

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 should be administered first.

Paclitaxel is administered in a 250-500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 1 hour.

Carboplatin should be administered in 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 paclitaxel or carboplatin. 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 restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel or carboplatin and appropriate therapy should be initiated.

Pre-medication

30 minutes prior to each paclitaxel infusion:
Chlorphenamine 10mg IV slow bolus
Dexamethasone 8mg IV slow bolus

Emetogenicity

EC cycles: moderate - high emetic potential

Carboplatin + paclitaxel weekly cycles: moderate - high emetic potential on day 1 and moderate emetic potential on days 8 and 15.

Additional supportive medication

Mouthwashes as per local policy
Proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered.

Primary GCSF prophylaxis:
EC: on days 2-8
Carboplatin + weekly paclitaxel: on days 3-5, days 10-12 and days 17-19.

Extravasation

Epirubicin is a vesicant (Group 5)
Cyclophosphamide is neutral (Group 1)
Carboplatin is an irritant (Group 3)
Paclitaxel is a vesicant (Group 5)

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 EC cycles

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

Investigations – pre subsequent carboplatin & paclitaxel cycles

Investigation	**Validity period** (or as per local policy)
FBC*	24 hours
U+E (including creatinine)	96 hours
LFTs	96 hours

*Additional FBC within 24 hours of day 8 and 15 doses.

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)
Bilirubin	≤ ULN
AST/ALT	≤2.0 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN

Dose modifications

- **Haematological toxicity**

EC cycles:

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 despite GCSF or neutrophils < 0.5 x 10_9/L for more than 1 week consider reducing doses to 80% for future cycles.

Carboplatin + weekly paclitaxel cycles:

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Carboplatin dose**	**Paclitaxel dose**
≥ 1.0	and	≥ 100	100%	100%
< 1.0	or	< 100	Delay 1 week (or until recovery) then reduce dose by 1 x AUC	Delay 1 week (or until recovery)*
< 1.0	and	< 100	Delay 1 week (or until recovery) then reduce by 1 x AUC	Delay 1 week (or until recovery) then reduce dose to 70mg/m2*

*Omit paclitaxel if occurring on **day 8 or 15**

In the case of febrile neutropenia (neutrophils < 0.5 × 10_9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 60mg/m^2 and carboplatin by 1 x AUC for all subsequent doses.

- **Renal impairment**

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

Epirubicin: There is no data available on use 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.

No dose modification required for paclitaxel.

- **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%
≥3 - 5	or	> 3.5	or	5-10	25%
> 5			or	> 10	Omit

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

Paclitaxel:
Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose. For more severe hepatic impairment, treatment may only proceed on consultant's decision, at a reduced dose with weekly monitoring of LFTs.

Carboplatin:
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**

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

Carboplatin + weekly paclitaxel:

Toxicity	**Definition**	**Carboplatin dose**	**Paclitaxel dose**
Fatigue	Grade 3	100%	1st occurrence – reduce to 70mg/m2 for all subsequent doses or omit.
Neuropathy	Grade 2	100%	1st occurrence – reduce to 70mg/m2 for all subsequent doses or omit.
	Grade ≥ 3		Discuss with consultant.

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
Teratogenicity
Infertility/Early menopause
Cardiotoxicity
Other primary cancer

- **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.

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.

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

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/m^2

References

- 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 Paclitaxel (Accord) accessed 28th April 2022 via www.medicines.org.uk
- Summary of Product Characteristics Carboplatin (Accord) accessed 28th April 2022 via www.medicines.org.uk
- Minckwitz, G et al. 2014. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol. 2014 15:747-56.
- Sikov, WM et al. 2015. Multivariate analysis of subtype and gene expression signatures predictive of pathological complete response (pCR) in triple-negative breast cancer (TNBC): CALGB 40603. JCO. 2015 33:13-21.

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