Paclitaxel and Carboplatin

Indication

Neoadjuvant or adjuvant treatment of early or locally advanced triple negative breast cancer where anthracyclines are not appropriate.

Palliative treatment for advanced breast cancer.

ICD-10 codes

Codes pre-fixed with C50.

Regimen details

Day	Drug	Dose	Route
1, 8 and 15	Paclitaxel	80mg/m²	IV infusion
1	Carboplatin	AUC 5	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

28 days

Number of cycles

6 cycles

Administration

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.

Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

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

This regimen has high emetic potential.

Additional supportive medication

H_2 antagonist or proton pump inhibitor if required.
Loperamide if required.
Mouthwashes as per local policy

Extravasation

Paclitaxel – vesicant (Group 5)
Carboplatin – 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
Calcium	14 days
Magnesium	14 days

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
Calcium	7 days
Magnesium	7 days

*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
Bilirubin	< 1.5 x ULN
AST/ALT	< 5 x ULN
Creatinine Clearance (CrCl)	> 30 mL/min (and < 10% change)

Dose modifications

- **Haematological toxicity**

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 dose by 1 x AUC	Delay 1 week (or until recovery) then reduce dose to 70mg/m^2.

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**

If calculated CrCl falls by >10% from previous dose, consider EDTA and / or dose recalculation.

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	EDTA then 100% dose (or consider changing to non-nephrotoxic regimen)
< 20	Contra-indicated

No dose modification required for paclitaxel.

- **Hepatic impairment**

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**

Toxicity	**Definition**	**Carboplatin dose**	**Paclitaxel dose**
Fatigue	Grade 3	100%	1st occurrence – reduce to 70mg/m^2 for all subsequent doses or omit.
Neuropathy	Grade 2	100%	1st occurrence – reduce to 70mg/m^2 for all subsequent doses or omit.
	Grade ≥ 3		Discuss with the consultant.
Arthralgia/Myalgia	Grade ≥ 2	100%	Consider diclofenac +/- co-codamol or prednisolone 10mg BD for 5 days starting 24 hours post paclitaxel. If persists reduce dose to 70mg/m^2.

For all other grade 3 toxicities (except alopecia and nausea and vomiting) withhold until grade ≤ 1 and continue with dose reduction of paclitaxel to 60mg/m^2 and carboplatin by 1 x AUC. If further toxicity discuss with consultant.

For any grade 4 toxicity (except alopecia and nausea and vomiting) withhold and discuss with consultant.

Adverse effects - for full details consult product literature/ reference texts

- **Rare or serious side effects**

Myelosuppression
Infertility
Teratogenicity
Hypersensitivity reactions
Pulmonary fibrosis
Nephrotoxicity
Electrolyte disturbances
Arrhythmias
Cardiac failure

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue

- **Other side effects**

Flu-like symptoms
Taste changes
Headache
Abdominal pain
Deranged liver function
Elderly patients may have a higher incidence of severe neuropathy, severe myelosuppression, or cardiovascular events compared to younger patients.

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.

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.

Carboplatin only:
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.

Additional comments

References

- Summary of Product Characteristics Carboplatin (Hospira) accessed 7 December 2016 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Hospira) accessed 7 December 2016 via www.medicines.org.uk
- Chen, X.S., et al. 2010. Weekly paclitaxel plus carboplatin is an effective non-anthracycline containing regimen as neoadjuvant chemotherapy for breast cancer. Annals of Oncology, 21;961-967

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