Carboplatin and Paclitaxel (Gynae/CUP)

Indication

Post-surgical adjuvant or neoadjuvant or relapse therapy for stage IC to IV ovarian, fallopian tube or primary peritoneal cancer.

First line or relapse therapy for advanced cervix, vaginal or vulval cancer not amenable to definitive radiotherapy or radio-chemotherapy.

First line adjuvant therapy for endometrial cancers (maximum 4 cycles) or neoadjuvant or relapse therapy for advanced endometrial cancers.

First line therapy for adenocarcinoma or undifferentiated cancers of uncertain primary site.

ICD-10 codes

Codes pre-fixed with C48, C51 - C57.

Regimen details

Day	Drug	Dose	Route
1	Paclitaxel	175mg/m²	IV infusion
1	Carboplatin	AUC 5 or 6*	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) a formal GFR measurement should be performed. If using a measured GFR consider dosing at AUC 5 and if using Cockcroft and Gault consider dosing at AUC 6.
CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

First line adjuvant treatment of endometrial cancer: 4 cycles
Other indications: 6 cycles
For neoadjuvant treatment, 3 cycles prior to surgery and then 3 cycles post surgery – to commence within 6 weeks of surgery.

Administration

Paclitaxel should be administered first.

Paclitaxel is administered in a 500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 3 hours.
Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Carboplatin should be administered in 250-500mL 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 16-20mg IV slow bolus

Consider administering hydrocortisone 100mg IV prior to carboplatin if there has been more than a 6 month gap between courses of treatment due to a possible reaction to carboplatin antibodies.

Emetogenicity

This regimen has moderate - high emetic potential.

Additional supportive medication

Proton pump inhibitor if required.
Loperamide if required.
Laxatives if required
Mouthwashes as per local policy

Extravasation

Carboplatin – irritant (Group 3)
Paclitaxel – vesicant (Group5)

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
CA125	28 days

Perform baseline measured GFR 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

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 x ULN

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

Dose modifications

Paclitaxel

Dose level	**Paclitaxel dose**
Full dose	175mg/m^2
First dose reduction	135mg/m^2
Second dose reduction	90mg/m^2
Third dose reduction	Discontinue

Carboplatin – reduce by dose by 1 x AUC

- **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 next dose reduction level.

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 135mg/m^2 and carboplatin by 1 x AUC for all future cycles.

- **Renal impairment**

If calculated CrCl falls by >10% from previous dose, consider dose recalculation.

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	Measured GFR then 100% dose (or consider changing to non-nephrotoxic regimen, discuss with consultant)
< 20	Discuss with consultant

- **Hepatic impairment**

Paclitaxel

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Paclitaxel dose**
≤1.25	and	<10	100%
1.25-2	and		135mg/m^2
2-5	and		90mg/m^2
> 5	or	≥10	Not recommended (consultant decision)

Carboplatin – no need for dose adjustment expected. Consultant decision if bilirubin > 5 x ULN or ALT ≥ 10 x ULN.

- **Other toxicities**

Toxicity	**Definition**	**Carboplatin dose**	**Paclitaxel dose**
Fatigue	Grade 3	100%	1st occurrence – 135mg/m^2, if persistent 90mg/m^2 or omit
Neuropathy	Grade 2	100%	1st occurrence – 135mg/m^2 for all future cycles, if persistent 90mg/m^2 or omit
	Grade ≥ 3		Withhold until ≤ Grade 1, restart at 90mg/m^2.
Arthralgia/My	Grade ≥ 2	100%	Consider diclofenac +/- co-codamol or prednisolone 10mg

algia			BD for 5 days starting 24 hours post paclitaxel. If persists reduce dose to 135mg/m^2

For all other grade 3 toxicities (except alopecia and nausea and vomiting) withhold until grade ≤ 1 and continue with carboplatin with 1 x AUC dose reduction and paclitaxel reduced to next dose reduction level. If further toxicity, consider additional dose reduction, 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
Hypersensitivity reactions
Pulmonary fibrosis
Nephrotoxicity
Electrolyte disturbances
Arrhythmias
Cardiac failure
Febrile Neutropenia

- **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
Rash
Ototoxicity
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 or DOAC 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, avoid concomitant use.

Paclitaxel is a CYP 2C8 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
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

In patients with significant frailty or co-morbidity where chemotherapy is considered appropriate and patients are carefully counselled about potential benefits and risks, consider strategies to minimise toxicity such as reducing the carboplatin dose to AUC 5 and paclitaxel to 135mg/m^2.

References

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