Carboplatin and Paclitaxel (gynae)

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 or relapse therapy for advanced inoperable for uterine papillary serous carcinoma or carcino-sarcoma (Malignant Mixed Mullerian Tumors) of the endometrium.

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)**
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. If using measured GFR, consider dosing at AUC 5. If using Cockcroft and Gault, consider dosing at AUC 6.
CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

6 cycles (for neoadjuvant treatment, 3 cycles prior to surgery and then 3 cycles post surgery – to commence within 6 weeks of surgery).
4 cycles for first line adjuvant treatment of endometrial cancer.

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 250mL glucose 5% over 30 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:

Ranitidine 50mg IV slow bolus
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

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	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

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

- **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 75%.

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 an carboplatin to 80% dose 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	EDTA then 100% dose (or consider changing to non-nephrotoxic regimen)
< 20	Contra-indicated

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Carboplatin dose**	**Paclitaxel dose**
<ULN	and	<5	100%	100%
1-1.5	and		100%	135mg/m^2
1.5-2.5	and		100%	75mg/m^2
2.5-4	and		80-100%	50mg/m^2
> 4	or	≥5	Not recommended (consultant decision)	

- **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/Myalgia	Grade ≥ 2	100%	Consider diclofenac +/- cocodamol or prednisolone 10mg 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 80% dose and paclitaxel 135mg/m^2. 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
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

In patients with significant frailty or co-morbidity where chemotherapy is nevertheless deemed appropriate, consider strategies to minimise toxicity such as reducing the carboplatin dose to AUC 3 and paclitaxel to 135mg/m^2.

References

- Summary of Product Characteristics Carboplatin (Hospira) accessed via www.medicines.org.uk (31 July 2014)
- Summary of Product Characteristics Paclitaxel (Hospira) accessed via www.medicines.org.uk (31 July 2014)
- Huebner G, Link H, Kohne CH, Stahl M, Kretzschmar A, Steinbach S, et al. German CUP Study Group. Paclitaxel and carboplatin vs gemcitabine and vinorelbine in patients with adeno- or undifferentiated carcinoma of unknown primary: a randomised prospective phase II trial. Br J Cancer 2009 100(1):44-9.
- Duska LR, Garrett A, Eltabbakh GH, Oliva E, Penson R, Fuller AF. Paclitaxel and Platinum Chemotherapy for Malignant Mixed Müllerian Tumors of the Ovary. Gynecol Oncol 2002 85 (3), 459-463.
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Written/reviewed by: Dr R Bowen (Consultant Oncologist, Royal United Hospital, Bath), Dr A Walther (Consultant Oncologist, UHBristol NHS Trust)

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

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

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