Carboplatin & Paclitaxel (Anal SCC)

Indication
First line palliative chemotherapy for patients with inoperable locally recurrent or metastatic anal squamous cell cancer (SCC).

ICD-10 codes
Codes pre-fixed with C21.

Regimen details

Day	Drug	Dose	Route
1, 8 and 15	Paclitaxel	80 mg/m2	IV infusion
1	Carboplatin	AUC5*	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 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 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 8mg IV slow bolus

Emetogenicity

This regimen has high emetic potential on day 1 and moderate emetic potential on days 8 and 15.

Additional supportive medication

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
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days

Consider baseline measured GFR if suspected or significant renal dysfunction

Investigations – pre subsequent cycles

Investigation	Validity period
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
Creatinine clearance	≥ 30ml/minute (and <10% change)
Bilirubin	< 1.5 x ULN
Alanine transaminase (ALT)or Aspartate transaminase (AST)	< 5 x ULN

Dose modifications

Paclitaxel dose levels

Starting dose	80mg/m2
Dose level -1	70mg/m2
Dose level -2	60mg/m2

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Carboplatin dose (Day 1)**	**Paclitaxel dose (Day 1)**	**Paclitaxel dose (Day 8 & 15)**
≥ 1.0	and	≥ 100	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)	Omit dose
< 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 all future doses by one dose level.	Omit dose

If haematological toxicity causing omission of a paclitaxel dose (day 8 ***or*** day 15) - no dose modification is required. If omission of both paclitaxel administrations (day 8 ***and*** day 15) doses of carboplatin and paclitaxel should be modified according to the day 8 or 15 blood count as per the table above.

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

CrCl (mL/min)	**Carboplatin dose**
>30ml	100%
20-30	Measured GFR then 100%. Consider alternative non-nephrotoxic regimen.
<20	Contraindicated

- **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**
Neuropathy	Grade 2	100%	Paclitaxel to be withheld until resolved to grade 1. Restart at a reduction of 1 dose level. If >2 week delay required, omit Paclitaxel from ongoing cycles.
	Grade 3-4		Paclitaxel should be omitted from subsequent cycles
Mucositis	Grade 2	100%	Delay until resolved to grade 1. No dose reduction required.
	Grade 3		Delay until resolved to grade 1. Dose reduce paclitaxel by one dose level in subsequent cycles. If mucositis persists at grade 3 for more than two weeks or recurs despite dose reduction, then paclitaxel should be omitted from subsequent cycles.
Fatigue	Grade 3	100%	1st occurrence – reduce by one dose level for all subsequent doses or omit.
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 by one dose level

For any grade 3 non-haematological toxicity, withhold until symptoms resolve to grade 1. On recovery, the causative chemotherapy agent should be reduced by 1 dose level in subsequent cycles.

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

- **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 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

Nil

References

- Summary of Product Characteristics Paclitaxel (Hospira) accessed via www.medicines.org.uk on 28th October 2021
- Summary of Product Characteristics Carboplatin (Hospira) accessed via www.medicines.org.uk on 28th October 2021
- Rao, S. *et al*. International Rare Cancers Initiative Multicenter randomized Phase II trial of cisplatin and fluorouracil versus carboplatin and paclitaxel in advanced anal cancer: InterAAct. J Clin Onc 38(22):2510-2518

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