Systemic Anti Cancer Therapy Protocol

Paclitaxel & Carboplatin Anal Cancer

PROTOCOL REF: MPHAPCAGA
(Version No: 2.1)

Approved for use in:

Metastatic or recurrent anal cancer

Dosage

Drug	Dose	Route	Frequency
Paclitaxel	**80mg/m²**	IV Infusion	Day 1, 8 and 15 of a 28 day cycle
Carboplatin	**AUC 5 x (GFR + 25)**	IV Infusion	Day 1 only of a 28 day cycle

For 6 cycles

Calvert formula for Carboplatin dosage

Carboplatin dose in mg = AUC 5 x (creatinine clearance + 25)

If estimated GFR is used the **Wright formula** must be used for creatinine clearance.

Creatinine clearance should be capped at 125mL/min for carboplatin

Avoid the use of Cockcroft and Gault formulae as it is less accurate.

Supportive Treatments:

Dexamethasone tablets 4mg orally twice daily for three days

Domperidone 10mg tablets, three times a day when required

Interactions

Aminoglycosides e.g. gentamicin: Increased risk of nephrotoxicity and ototoxicity with carboplatin. Renal function should be well monitored and audiometric tests carried out as indicated.

Antiepileptics (CYP 3A4 inducers): Carboplatin can cause a decrease in phenytoin serum levels. This may lead to reappearance of seizures and may require an increase of phenytoin dosages.

Phenytoin, carbamezapine and phenobarbital increase the clearance of paclitaxel and increase its maximum tolerated dose.

Ciclosporin: Levels of paclitaxel increased after oral administration of ciclosporin.

Fluconazole/Ketoconazole (CYP3A4 inhibitors): Paclitaxel level may be increased

Quinine and Verapamil: Paclitaxel level possibly increased.

Warfarin: The effects of warfarin may be increased. Monitor INR closely.

Extravasation risk

Paclitaxel: vesicant

Carboplatin: irritant

Refer to Clatterbridge Policy 'Prevention and Management of Extravasation Injuries' for further guidance.

Administration

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	6.6mg	IV bolus	30 minutes before chemotherapy
1	Ondansetron	16mg	Oral	30 minutes before chemotherapy
1	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy (for the first three cycles – can be discontinued for those patients who do not experience a hypersensitivity reaction)
1	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy
1	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250mL/500mL sodium chloride 0.9% over 60 minutes**
1	**Carboplatin**	**AUC 5**	**IV Infusion**	**500mL glucose 5% over 30 to 60 minutes**
8	Dexamethasone	6.6mg	IV bolus	30 minutes before chemotherapy
8	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy (see above)

8	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy
8	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250mL/500mL sodium chloride 0.9% over 60 minutes**
15	Dexamethasone	6.6mg	IV bolus	30 minutes before chemotherapy
15	Famotidine	20mg	Oral	At least 60 minutes before chemotherapy (see above)
15	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy
15	**Paclitaxel**	**80mg/m²**	**IV Infusion**	**250mL/500mL sodium chloride 0.9% over 60 minutes**

- Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.
- Paclitaxel should be administered prior to carboplatin
- Paclitaxel in solution may show haziness which is attributed to the formulation of paclitaxel.
- Excessive shaking, agitation, or vibration of paclitaxel may induce precipitation and should be avoided
- Facilities to treat anaphylaxis must be present when administering this regime. If a patient experiences an **infusion-related reaction**, give future does with premedication cover of IV chlorphenamine 10mg and IV hydrocortisone 100mg.
- Premedication treatment of chlorphenamine, dexamethasone and famotidine is given prior to paclitaxel to reduce the risk of hypersensitivity. Paclitaxel reactions commonly occur within the first few minutes of starting the infusion most likely with the first two cycles. Carboplatin risk of hypersensitivity and anaphylaxis may increase with previous exposure to platinum therapy.
- Famotidine can be stopped after three cycles for those patients who do not experience a drug hypersensitivity reaction.

Hypersensitivity

As with all platinum and paclitaxel based chemotherapy, patients may experience allergic reaction during administration. The infusion should be stopped and the following should be administered.

- Hydrocortisone 100 to 200mg IV
- Chlorphenamine 10 mg IV

Refer to the Trusts Hypersensitivity Guidelines for further information.

It should be strongly noted that patients who have severe reactions should not be re-challenged.

Main Toxicities

Cardiac and Vascular disorders	Risk of bradycardia and hypotension is common with paclitaxel
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis
General disorders and administration site conditions	Malaise, fever, chills, urticaria, flu-like syndrome, rash, pruritus. **Carboplatin:** Decreases in serum electrolytes (sodium, magnesium, potassium and calcium) Hyperuricaemia: Serum levels of uric acid can be decreased by allopurinol. **Paclitaxel:** Injection site reactions (including localized oedema, pain, erythema, induration, on occasion extravasation can result in cellulitis, skin fibrosis and skin necrosis) Severe elevation in aspartate aminotransferase (AST) and alkaline phosphatase.
Haematological	Neutropenia, anaemia, thrombocytopenia
Infections/Infestations	Paclitaxel: Infection (mainly urinary tract and upper respiratory tract infections) are very common, with reported cases of fatal outcome
Musculoskeletal	Arthralgia, myalgia common with paclitaxel
Nervous system	Carboplatin: Paraesthesia and decreased deep tendon reflexes. Paclitaxel: peripheral neuropathy is very common
Ototoxicity	Hearing loss
Skin and subcutaneous tissue disorders	Alopecia Allergic skin rash frequently associated with pruritus
Urological	Carboplatin: Renal function impairment

Investigations

	Cycle 1 to 6				
	Pre	**Day 1**	**Day 8**	**Day 15**	**Comments**
Clinical Assessment	X			Check booked post cycle 3 & post cycle 6	
SACT Assessment	X	X	X	X	
FBC	X	X	X	X	
U&E & LFT	X	X	X	X	
Mg^{2+}	X	X	X	X	
CrCl/Urine output	X	X	X	X	
CT scan	X			Check booked post cycle 3 & post cycle 6	
ECG					If clinically indicated
BP	X				If clinically indicated
Respiratory rate					If clinically indicated
Informed Consent	X				
Height Recorded	X				
Weight recorded	X	X	X	X	
Blood glucose	X				If clinically indicated

Dose Modifications and Toxicity Management

Haematological Toxicity

Proceed on day 1 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Delay 1 week on day 1 if-

Plt ≤ 99 x 10^9/L	ANC ≤ 0.9 x 10^9/L

Proceed on day 8 and 15 if-

Plt ≥ 100 x 10^9/L	ANC ≥ 1.0 x 10^9/L

Omit day 8 or day 15 if toxicity occurs – do not delay

Non Haematological Toxicity

Grading and Management of Toxicity

Toxicity should be grading according to the CTCAE v4.0 criteria. Following assessment treatment should be withheld for any toxicity until resolved to grade 0/1. For dose modification, follow the general guidance below and discuss with treating clinician.

Omit day 8 or day 15 if toxicity occurs – do not delay

Peripheral Neuropathy

Paclitaxel
CTCAE grade 2 peripheral neuropathy: withhold paclitaxel only until the neuropathy recovers to grade 1 then dose reduce to 75% of the original dose. Where the peripheral neuropathy is ≥ grade 3 omit paclitaxel from subsequent cycles.

Hepatic Impairment

Carboplatin
No dose adjustment is necessary

Paclitaxel
Patients with severe hepatic impairment must not be treated with paclitaxel. Continued on next page…

Paclitaxel

Patients with severe hepatic impairment must not be treated with paclitaxel.

Patients with hepatic impairment may be at increased risk of toxicity, particularly grade III-IV myelosuppression. There is no evidence that the toxicity of paclitaxel is increased when given as a 3-hour infusion to patients with mildly abnormal liver function. No data are available for patients with severe baseline cholestasis.
Patients should be monitored closely for the development of profound myelosuppression.

Bilirubin /µmol/l	Dose in mg/m^2
< 26	80
27 to 51	65
>51	withhold

Renal Impairment

Carboplatin

Patients' with creatinine clearance values of less than 60 ml/min are at greater risk to develop myelosuppression. Carboplatin is contraindicated if glomerular filtration rate is ≤ 20 ml/min.

The optimal use of Carboplatin in patients presenting with impaired renal function requires adequate dosage adjustments and frequent monitoring of both haematological nadirs and renal function.

In patients with impaired renal function, dosage of carboplatin should be reduced (refer to Calvert formula).

Paclitaxel

No dose adjustment necessary

References

Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)

Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)

Rao S, Sclafani F, Eng C, et al, 2018. *InterAACT: A multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatment naïve disease - An International Rare Cancers Initiative (IRCI) trial.* ESMO (European Society for Medical Oncology) 2018 Congress, Munich, Germany, 19 – 23 October 2018