Systemic Anti Cancer Treatment Protocol

Paclitaxel & Carboplatin Gynaecological Cancer

PROTOCOL REF: MPHAGYNPCA
(Version No: 1.1)

Approved for use in:

- 1st line treatment for stage Ib-IV with minimal residual disease/ bulk residual disease patients with advanced/ adjuvant ovarian cancer.
- 2nd line treatment for advanced or metastatic ovarian cancer.
- 1st line epithelial ovarian cancer with mucinous histology
- Advanced endometrial carcinoma
- Recurrent/metastatic cervical cancer

Dosage

Drug	Dose	Route	Frequency
Paclitaxel	**175mg/m²**	IV Infusion	21 days
Carboplatin	***AUC 5/6 x (GFR + 25)**	IV Infusion	

***AUC 5/6 depending on protocol and clinical situation**

Calvert formula for Carboplatin dosage

Carboplatin dose in mg = AUC 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 the network guidance for the prevention and management of extravasation

Administration

Day	Drug	Dose	Route	Diluent and rate
1	Dexamethasone	20mg	IV bolus	30 minutes before chemotherapy
1	Ondansetron	16mg	Oral	30 minutes before chemotherapy
1	Ranitidine	50mg	IV bolus	30 minutes before chemotherapy
1	Chlorphenamine	10mg	IV bolus	30 minutes before chemotherapy

1	**Paclitaxel**	**175mg/m²**	**IV Infusion**	**500mL sodium chloride 0.9% over 3 hours**
1	**Carboplatin**	**AUC 5/6**	**IV Infusion**	**500mL glucose 5% over 30 to 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 ranitidine 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.

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

	Pre	Cycle 1	Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Ongoing
Medical Assessment	X				X			After cycles 3 and 6 then as per management plan
SACT Assessment	X	X	X	X	X	X	X	Every cycle
FBC	X	X	X	X	X	X	X	Every cycle
U&E & LFT	X	X	X	X	X	X	X	Every cycle
CrCl/Urine output	X	X	X	X	X	X	X	Every cycle
CA125*	X	X	X	X	X	X	X	Every cycle *ovarian patients only
CT scan	X				X			After cycles 3 and 6
Informed Consent	X							
PS recorded	X	X	X	X	X	X	X	Every cycle
Toxicities documented	X	X	X	X	X	X	X	Every cycle
Weight recorded	X	X	X	X	X	X	X	Every cycle

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

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.

	Grade 2	Grade 3	Grade 4
1st appearance	Interrupt treatment until resolved to grade 0/1, then continue at 100% of original dose with prophylaxis where possible	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose or AUC 4 with prophylaxis where possible	Discontinue treatment
2nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose or AUC 4	Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose or AUC 3.5	
3rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose or AUC 3.5	Discontinue treatment	
4th appearance	Discontinue treatment		

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. 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	135
27 to 51	75
>51	50

If bilirubin < 1.25 x ULN and transaminase < 10 x ULN, dose at 175 mg/m^2

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).

References

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

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