Systemic Anti Cancer Treatment Protocol

Cisplatin & Paclitaxel
Gynaecological Cancer

PROCTOCOL REF: MPHAGYNCIP
(Version No: 1.2)

Approved for use in:

- First line treatment for stage Ib-IV with minimal residual disease/ bulk residual disease patients with advanced ovarian cancer (as alternative to carboplatin combination regimen)
- Recurrent/metastatic cervical cancer – greater than 6 months from completion of chemo-radiation to relapse.

Creatinine clearance must be above 50mL/min prior to start of treatment

Dosage

Ovarian Regimen

Drug	Dose	Route	Frequency
Paclitaxel	**175mg/m²**	IV Infusion	21 days max 6 cycles
Cisplatin	**50mg/m²**	IV Infusion	

Cervical Regimen

Drug	Dose	Route	Frequency
Paclitaxel	**135mg/m²**	IV Infusion	21 days max 6 cycles
Cisplatin	**50mg/m²**	IV Infusion	

Supportive treatments:

Dexamethasone 4mg orally twice daily for 3 days

Domperidone 10mg orally three times a day when required

Interactions

Oral anticoagulants:

In the event of simultaneous use of oral anticoagulants, it is advisable regularly to check the INR.

Anticonvulsive substances:

Serum concentrations of anticonvulsive medicines may remain at sub therapeutic levels during treatment with cisplatin. Cisplatin may reduce the absorption of phenytoin resulting in reduced epilepsy control when phenytoin is given as current treatment.

Aminoglycosides e.g. gentamicin - Increased risk of nephrotoxicity and ototoxicity

Extravasation risk

Paclitaxel and cisplatin are both vesicants.

Administration

Day	Drug	Dose	Route	Diluent and rate
1	Chlorphenamine	10mg	IV Infusion	30 minutes prior to paclitaxel
1	Dexamethasone	20mg	IV Infusion	30 minutes prior to paclitaxel
1	Famotidine	20mg	Oral	At least 60 minutes prior to paclitaxel (can be discontinued after three cycles for those patients who do not experience a hypersensitivity reaction)
1	**Paclitaxel**	**175mg/m² or 135mg/m²**	**IV**	In 500mL sodium chloride 0.9% over 3 hours (administer using a non-PVC giving set with a 0.22 micron filter)
1	Furosemide	20mg	oral	
1	Aprepitant	125mg	oral	1 hour before cisplatin
1	Ondansetron	16mg	oral	30 minutes prior to cisplatin
1	Sodium Chloride 0.9%1000mL (+ 20mmol Potassium Chloride)		IV Infusion over 90 minutes	

	Measure urine output volume and record **If urine output averages 100mL/hour over previous 3 hours then proceed with cisplatin infusion** **If urine output is less than 100mL/hour the patient should be assessed and further 500mL sodium chloride 0.9% given IV over 30 minutes**			
1	**Cisplatin**	**50mg/m^2**	**IV**	in 1000mL Sodium Chloride 0.9% over 90 minutes
1	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)		IV Infusion over 90 minutes	

Paclitaxel

- Paclitaxel must be administered using a non-PVC giving set with a 0.22 micron filter.
- 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.
- Famotidine can be stopped after three cycles for those patients who do not experience a drug hypersensitivity reaction.

Hypersensitivity

Cisplatin and Paclitaxel
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.

Cisplatin Dose Guidelines

Cisplatin is nephrotoxic and thus patients must have their renal function measured prior to each cycle.

Creatinine clearance	Cisplatin dose
> 50mL/min	100%
40 to 50 mL/min	75%
< 40mL/min	no further cisplatin

Main Toxicities

Cisplatin and Paclitaxel	
Cardiac disorders	Arrhythmia, bradycardia, tachycardia, hypotension
Gastrointestinal	Nausea, vomiting, diarrhoea, constipation, mucositis.
General	Malaise, fever, chills, urticaria, flu-like syndrome, rash, pruritus, alopecia **Paclitaxel** - Severe elevation in aspartate aminotransferase (AST) severe elevation in alkaline phosphatase. **Cisplatin** - Dehydration, hypokalaemia, hypophosphataemia, hypocalcaemia, tetany, muscle spasms
Haematological	Neutropenia, anaemia, thrombocytopenia
Hypersensitivity reactions	Skin rash, urticaria, erythematous rash, and fever with no apparent cause or pruritus
Musculoskeletal	Arthralgia, myalgia
Nervous system	Peripheral neuropathy
Ototoxicity	Ototoxicity is common with cisplatin and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000Hz). Decreased ability to hear conversational tones may occur occasionally.
Respiratory	Cisplatin - dyspnoea, pneumonia, respiratory failure

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
Mg^{2+}	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:-

Platelets ≥ 100	ANC ≥ 1.0

Delay 1 week on day 1 if:-

Platelets ≤ 99	ANC ≤ 0.9

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 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	Discontinue treatment
2nd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 75-80% of original dose	Interrupt treatment until resolved to grade0/1, then continue at 50% of original dose	
3rd appearance	Interrupt treatment until resolved to grade 0/1, then continue at 50% of original dose	Discontinue treatment	
4th appearance	Discontinue treatment		

Peripheral Neuropathy

Paclitaxel
NCI-CTC 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 again withhold the paclitaxel until it resolves to grade one and then reduce the dose of paclitaxel to 50%. Paclitaxel should be discontinued if the neuropathy does not resolve to grade one.

Cisplatin
Severe cases of neuropathies have been reported. These neuropathies may be irreversible and may manifest by paresthesia, areflexia and a proprioceptive loss and a sensation of vibrations. A loss of motor function has also been reported. A neurologic examination must be carried out at regular intervals. Special caution must be exercised for patients with peripheral neuropathy not caused by cisplatin. Prior to each course, the absence of symptoms of peripheral neuropathy should be established.

Neurotoxicity/Ototoxicity

Cisplatin
If patient develops Grade 2 neuropathy or ototoxicity, discuss with Consultant. Patients with functional hearing loss should have cisplatin omitted; carboplatin AUC 3-5 can be substituted.

Hepatic Impairment

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

References

1. **https://www.medicines.org.uk/emc/medicine/**

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

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

4. Stockley's drug interactions. Ninth edition. Edited K. Baxter. Pharmaceutical press. London. 2010