Chemotherapy Protocol

GYNAECOLOGICAL CANCER

CARBOPLATIN (AUC5)-CISPLATIN-PACLITAXEL RT

Regimen

- Endometrial-Carboplatin (AUC5)-Cisplatin-Paclitaxel RT

Indication

- The treatment of endometrial carcinoma
- WHO performance status 0, 1, 2

Toxicity

Drug	Adverse Effect
Carboplatin	Thrombocytopenia, peripheral neuropathy, nephrotoxicity at high doses, electrolyte disturbances
Cisplatin	Neuropathy, nephrotoxicity, ototoxicity
Paclitaxel	Hypersensitivity, hypotension, bradycardia, peripheral neuropathy, myalgia and back pain on administration

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Monitoring

Drugs

- FBC, LFTs and U&Es prior to day one each cycle
- EDTA or calculated creatinine clearance prior to each cycle

Dose Modifications

The dose modifications listed are for haematological, liver and renal function and drug specific toxicities only. Dose adjustments may be necessary for other toxicities as well.

In principle all dose reductions due to adverse drug reactions should not be re-escalated in subsequent cycles without consultant approval. It is also a general rule for chemotherapy that if a third dose reduction is necessary treatment should be stopped.

Please discuss all dose reductions / delays with the relevant consultant before prescribing, if appropriate. The approach may be different depending on the clinical circumstances.

Haematological

Consider blood transfusion if patient symptomatic of anaemia or has a haemoglobin of less than 8g/dL.

Prior to each cycle the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1.5x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Cisplatin

Toxicity	Adjustment	Remarks
Haematological		
Neutrophil less than $1.5x10^9$/L	Delay for 7 days	If recovery requires longer than 7 days stop the cisplatin
Platelets less than $100x10^9$/L	Delay for 7 days	If recovery requires longer than 7 days stop the cisplatin
Renal Toxicity		
GFR less than 50ml/min or 40mL/min measured creatinine or EDTA)	Delay for 7 days	If recovery requires longer than 7 days stop the cisplatin. Do not use if the creatinine clearance as calculated by Cockroft is less than 40mL/min
Neurological		
Neuropathy 2 or greater	Stop the cisplatin	

Carboplatin and Paclitaxel

Neutrophils ($x10^9$/L)	Dose Modifications (carboplatin and paclitaxel)
1.5 or greater	100%
less than 1.5	Delay for 7 days. If the counts recover to at least $1.5x10^9$/L within this time continue with the full dose. If the counts recover to $1x10^9$/L resume treatment but add in growth factors. If the neutrophils do not recover to more than $1.5x10^9$/L by the third week or if there is a second recurrence (with dose reduction) of neutrophils less than $1.5x10^9$/L not resolving after 14 days then discontinue carboplatin and continue with single paclitaxel.
Platelets ($x10^9$/L)	**Dose Modifications (carboplatin and paclitaxel)**
100 or above	100%
50-99	Delay for 7 days. If the counts recover to at least $100x10^9$/L within this time then continue with the full dose. If counts recover within 14 days the continue with the full dose of paclitaxel but reduce the dose of carboplatin to AUC 4. If counts do not recover within 7 days or repeated delays are required then delay until recovery then reduce dose by 20%
less than 50	Delay until recovery then reduce dose by 50%

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT units	Dose
Carboplatin	N/A		N/A	No dose adjustment needed
Cisplatin	N/A		N/A	No dose adjustment needed
Paclitaxel	less than 21	and	less than 10xULN	175mg/m^2
	21-26			135mg/m^2
	27-51			75mg/m^2
	52-85			50mg/m^2
	greater than 85	or	greater than 10xULN	Contra indicated

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose
Carboplatin*	less than 20	Omit
Cisplatin	Less than 40mL/min	Do not use if the creatinine clearance as calculated by Cockroft is less than 40mL/min
Paclitaxel	N/A	No dose adjustment needed

* Significant changes in GFR of more than 10% may require dose adjustment.

Other

Dose reductions or interruptions in therapy are not necessary for those toxicities that are considered unlikely to be serious or life threatening. For example, alopecia, altered taste or nail changes.

For all other non-haematological NCI-CTC grade 3 and above toxicities delay treatment until the adverse effect has resolved to NCI-CTC grade 1 or below. The dose of the causative agent should then be reduced to 75% of the original dose or discontinued as appropriate.

Regimen

Cisplatin

The first concurrent cycle of cisplatin should be given within days 1-3 of radiotherapy and the second cycle 3 weeks after the first cycle (4th week of radiotherapy, within days 22-24, 16-18

of radiotherapy fractions). It will be set as a 21 day cycle for 2 cycles. The dates can be adjusted to fit with radiotherapy. On occasion the MDT may recommend giving the carboplatin-paclitaxel prior to the cisplatin-radiotherapy. For example if the risk of metastasis is significantly greater than that of local recurrence.

21 day cycle for 2 cycles

Drug	Dose	Days	Administration
Cisplatin	50mg/m^2	1	Intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride over a minimum of 120 minutes. The maximum rate is 1mg/mL.

21 day cycle for 4 cycles

Adjuvant carboplatin and paclitaxel should be started within 3 weeks after termination of radiotherapy, and preferably 3-4 weeks after the last administration of cisplatin. There will be a 21 day gap set up in ARIA, the start date can be adjusted as necessary.

Before starting adjuvant carboplatin and paclitaxel, the toxicity of the concomitant chemo-radiotherapy should be resolved to less than grade 2.

AUC for carboplatin should in principle be recalculated at each cycle but should at least be recalculated in case of increasing serum creatinine (increase of 10% and/or out of normal range) and/or weight changes.

Drug	Dose	Days	Administration
Carboplatin	AUC5 (maximum dose 790mg)	1	Intravenous infusion in 500ml glucose 5% over 60 minutes
Paclitaxel	175mg/m^2	1	Intravenous infusion in 500ml sodium chloride 0.9% over 180 minutes.

Dose Information

- The recommended maximum dose when using a calculated creatinine clearance at AUC5 is 750mg (creatinine clearance 125ml/min). This is not a dose included in the national dose banding table. The maximum dose has been set at 790mg in ARIA. Please check if this dose is appropriate. If you have an obese patient or an individual with a calculated creatinine clearance above 125ml/min please seek advice from the relevant consultant.

- It should be noted that the dose of carboplatin may need to be altered if there is a change (improvement or reduction) in renal function of more than 10% from the previous cycle.

- Carboplatin will be dose banded in accordance with the national dose bands (10mg/ml)
- The maximum dose of carboplatin for AUC 5 is 750mg. This will be set as 790mg in ARIA to comply with national dose bands.
- Cisplatin will be dose banded in accordance with the national dose bands (1mg/mL)
- Paclitaxel will be dose banded in accordance with the national dose bands (6mg/mL)

Administration Information

Extravasation

- Carboplatin – irritant
- Cisplatin - exfolliant
- Paclitaxel - vesicant

Other

- Hypersensitivity reactions tend to occur with the first or second infusion of paclitaxel. Paclitaxel infusion should be interrupted for minor symptoms such as flushing or localised rashes. If these resolve promptly (within 5 minutes) the infusion may be restarted at a lower rate with intensive monitoring. Immediately discontinue the infusion for server reactions which include profound hypotension, bronchospasm and generalised erythema.
- Paclitaxel must be administered via a non-PVC administration set containing an in-line 0.22 micron filter.

Additional Therapy

- Cisplatin

  Antiemetics

  15-30 minutes prior to chemotherapy

  - aprepitant 125mg oral
  - dexamethasone 4mg
  - ondansetron 8mg

  As take home medication

  - aprepitant 80mg once a day for 2 days starting on day two of the cycle oral
  - dexamethasone 4mg once a day for 3 days starting on day two of the cycle oral
  - ondansetron 8mg twice a day for 3 days starting on the evening of day 1 oral
  - metoclopramide 10mg three times a day when required oral

Cisplatin pre and post hydration as follows;

Pre

Furosemide 40mg oral or intravenous

1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes
Post

1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes

Patients should be advised to drink at least 3 litres of fluid in the 24 hours after administration of cisplatin.

- Carboplatin and Paclitaxel

Premedication to reduce of risk of hypersensitivity reaction

30 minutes before chemotherapy

- chlorphenamine 10mg intravenous
- dexamethasone 20mg oral or intravenous
- H_2 antagonist according to local formulary choice and availability

Antiemetics

15-30 minutes prior to chemotherapy

- ondansetron 8mg oral or intravenous

As take home medication

- dexamethasone 4mg oral twice a day for 3 days
- metoclopramide 10mg oral three times a day as required

Gastric protection with a proton pump inhibitor or a H_2 antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

References
1. PORTEC Trial Protocol. Randomized phase III Trial Comparing Concurrent Chemoradiation and Adjuvant Chemotherapy with Pelvic Radiation Alone in High Risk and Advanced Stage Endometrial Carcinoma: PORTEC-3. Trial Protocol Version 12 April 2012.

REGIMEN SUMMARY

Carboplatin (AUC5)-Cisplatin-Paclitaxel RT

Cisplatin day 1

1. Aprepitant 125mg oral
   Administration instructions: administer 15-30 minutes before SACT

2. Dexamethasone 4mg oral or intravenous equivalent dose
   Administration instructions: administer 15-30 minutes before SACT

3. Ondansetron 8mg oral or intravenous
   Administration instructions: administer 15-30 minutes before SACT

4. Furosemide 40mg oral or intravenous
   Administration instructions: To be administered prior to pre-hydration. This may be given as furosemide 40mg IV stat if required.

5. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes
   Administration instructions: Monitor fluid balance, urine output and weight

6. Cisplatin 50mg/m^2 intravenous infusion in 1000ml sodium chloride 0.9% with 20mmol potassium chloride at a maximum rate of 1mg cisplatin/minute (minimum time 120 minutes)

7. 1000ml sodium chloride 0.9% with 20mmol potassium chloride and 16mmol magnesium sulphate over 60 minutes
   Administration instructions: Monitor fluid balance, urine output and weight

Take Home Medicines (day

1. Aprepitant 80mg once a day for two days starting on the day after cisplatin oral
   Administration Instructions
   Take 80mg once a day for two days starting on the day after cisplatin

2. Dexamethasone 4mg once a day for three days starting on the day after cisplatin oral
   Administration Instructions
   Take 4mg once a day for three days starting on day after cisplatin

3. Ondansetron 8mg twice a day for three days starting on the evening of the day of cisplatin administration
   Administration Instructions
   Take 8mg twice a day for three days starting on the evening of the day of cisplatin administration

4. Metoclopramide 10mg three times a day when required oral
   Administration Instructions
   Please supply 28 days or an original pack

Carboplatin-Paclitaxel

Day 1

1. Chlorphenamine 10mg intravenous
   Administration instructions: administer 30 minutes before SACT

2. Dexamethasone 20mg intravenous
   Administration instructions: administer 30 minutes before SACT

3. H_2 antagonist according to local formulary choice and availability
   Administration Instructions:
   Administer according to local formulary choice and availability one of the following 30 minutes prior to chemotherapy;
   - famotidine 20mg oral once only
   - nizatidine 150mg oral once only
   - ranitidine 150mg oral once only
   - ranitidine 50mg intravenous once only

   There are stock shortages of H_2 antagonists. The administration may proceed without these agents being given unless there is a specific instruction from the prescriber in the ARIA journal that a H_2 antagonist must be administered. Many Trusts do not administer an H_2 antagonist from cycle three onwards. They have been left in the ARIA protocols so that decisions can be made on an individual Trust and patient basis.

4. Ondansetron 8mg oral or intravenous
   Administration instructions: administer 15-30 minutes before SACT

5. Paclitaxel 175mg/m^2 in 500ml sodium chloride 0.9% intravenous infusion over 180 minutes.
   Administration instructions: Administer via a non-PVC administration set containing an in-line 0.22 micron filter.

6. Warning - Carboplatin Maximum Dose
   Administration Instructions
   The dose of carboplatin is capped at a creatinine clearance of 125ml/min. The internationally recommended maximum dose of carboplatin for AUC 5 is 750mg. The national dose bands do not contain this dose so the cap has been set at 790mg in ARIA. Please check this dose is appropriate for your patient.

7. Carboplatin AUC 5 (maximum dose 790mg) intravenous infusion in 500ml glucose 5% over 60 minutes.

Take Home Medicines

8. Dexamethasone 4mg oral twice a day for three days starting the day after chemotherapy

9. Metoclopramide 10mg oral three times a day for three days then 10mg three times a day when required for nausea
   Administration Instructions
   Please supply 28 tablets or an original pack as appropriate

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.1	May 2023	Carboplatin amended with national dose bands and maximum dose amended. Administration instructions added to regimen summary Warning added	Alexandra Pritchard Pharmacist	Tom Hurst Pharmacy Technician
1	Feb 2021	None	Dr Deborah Wright Pharmacist	Dr V McFarlane Consultant Clinical Oncologist Dr R Tarrant Consultant Clinical Oncologist

This chemotherapy protocol has been developed as part of the chemotherapy electronic prescribing project. This was and remains a collaborative project that originated from the former CSCCN. These documents have been approved on behalf of the following Trusts;

Hampshire Hospitals NHS Foundation Trust
NHS Isle of Wight
Portsmouth Hospitals NHS Trust
Salisbury NHS Foundation Trust
University Hospital Southampton NHS Foundation Trust
Western Sussex Hospitals NHS Foundation Trust

All actions have been taken to ensure these protocols are correct. However, no responsibility can be taken for errors which occur as a result of following these guidelines.