Chemotherapy Protocol

GYNAECOLOGICAL CANCER

CARBOPLATIN (AUC5) - DOXORUBICIN PEGYLATED LIPOSOMAL (Caelyx)

Please note this protocol is based on information for the use of the Caelyx brand of doxorubicin pegylated liposomal. Brands may not be interchangeable.

Regimen

- Ovary – Carboplatin (AUC5)- Doxorubicin pegylated liposomal (Caelyx)

Indication

- Second line or subsequent treatment of platinum sensitive or partially platinum-sensitive relapsed ovarian cancer in patients previously treated with a taxane/platinum regimen.
- WHO performance status 0,1, 2
- Palliative intent

Toxicity

Drug	Adverse Effect
Carboplatin	Thrombocytopenia, peripheral neuropathy, nephrotoxicity at high doses, electrolyte disturbances
Doxorubicin pegylated liposomal	Palmar plantar erythrodysthesia (hand and foot syndrome), rash, GI disturbances, cardiotoxicity, asthenia, paresthesia

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

Monitoring

Drugs

- FBC, LFT's and U&E's prior to each cycle
- EDTA or calculated creatinine clearance prior to each cycle
- CA125 prior to each cycle
- Ensure adequate cardiac function before starting therapy. Baseline ECG and LVEF should be measured in patients with a history of cardiac problems or in the elderly. Discontinue doxorubicin pegylated liposomal if cardiac failure develops

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 cycle 1 the following criteria must be met;

Criteria	Eligible Level
Neutrophil	equal to or more than $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Day 1

Neutrophils ($x10^9$/L)	Dose Modifications (carboplatin and doxorubicin pegylated liposomal)
1 or greater	100%
less than 1	Delay one week. If the counts have recovered to $1x10^9$/L or greater at this point continue with doxorubicin pegylated liposomal 25mg/m^2 and carboplatin AUC 4.
0.5 or below for at least 7 days or febrile neutropenia	Delay until recovery to $1x10^9$/L or greater then continue with doxorubicin pegylated liposomal at 25mg/m^2 and carboplatin AUC 4.
Platelets ($x10^9$/L)	**Dose Modifications (carboplatin and doxorubicin pegylated liposomal)**
100 or greater	100%
less than 100	Delay one week. If recovery to $100x10^9$/L or greater at this point continue with doxorubicin pegylated liposomal at 25mg/m^2 and carboplatin AUC 4.
less than 25 or bleeding	Delay until recovery to 100 $x10^9$/L or greater then continue with doxorubicin pegylated liposomal 25mg/m^2 and carboplatin AUC 4.

Hepatic Impairment

The doses recommended below are for initial dosing. If the first dose of doxorubicin pegylated liposomal is well tolerated with minimal toxicity and no increase in bilirubin or liver enzymes the dose may be increased from *75% to 100% and from **50% to 75% at the next cycle (and from** 75% to 100% on subsequent cycles where appropriate.)

Drug	Bilirubin µmol/L		AST/ALT units	Dose (% of original dose)
Doxorubicin pegylated liposomal	20 or less			100%
	21-51			75%*
	51 or greater			50%**
Carboplatin	N/A		N/A	No dose adjustment needed

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Doxorubicin pegylated liposomal	30 or greater	No dose modification needed
	Less than 30	Clinical decision
Carboplatin	Less than 20	Omit

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(s) should then be reduced to 75% of the original dose or discontinued as appropriate.

Doxorubicin Pegylated Liposomal

Palmer-Plantar Erythrodesia / Stomatitis			
NCI-CTC Toxicity Grade	**Number of Weeks after the Dose of doxorubicin pegylated liposomal**		
	4	**5**	**6**
1	Re-dose unless patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	Re-dose unless patient has experienced a previous grade 3 or 4 skin toxicity, in which case wait an additional week	Decrease dose by 25 % and return to 4 week interval or stop treatment
2	Wait an additional week	Wait an additional week	Decrease dose by 25 % and return to 4 week interval or stop treatment
3	Wait an additional week	Wait an additional week	Stop treatment
4	Wait an additional week	Wait an additional week	Stop treatment

Regimen

The starting dose of carboplatin AUC 5 is used with calculated GFR. AUC 4 may be considered with EDTA clearance, seek advice from the appropriate consultant before prescribing. The recommended maximum dose when using a calculated creatinine clearance at AUC 5 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.

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

28 day cycle for 6 cycles

Drug	Dose	Days	Administration
Carboplatin	AUC 5 (max dose 790mg)	1	Intravenous infusion in 500ml glucose 5% over 60 minutes.
Doxorubicin pegylated liposomal	30mg/m^2	1	Intravenous infusion in 250ml glucose 5%. (The first infusion to be given at a maximum rate of 1mg/minute. If well tolerated subsequent infusions may be given over 60 minutes.)

Dose Information

- 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.
- 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.
- Doxorubicin pegylated liposomal will be dose banded in accordance with the national dose bands (2mg/ml)
- The maximum lifetime cumulative dose of doxorubicin is 450mg/m^2. However prior radiotherapy to mediastinal/pericardial area should receive a lifetime cumulative doxorubicin dose of no more than 400mg/m^2. Also consider previous anthracycline exposure.

Administration Information

Extravasation

- Carboplatin – irritant
- Doxorubicin pegylated liposomal – exfoliant

Other

- The first infusion of doxorubicin pegylated liposomal is to be given at a maximum rate of 1mg/minute. If this is well tolerated subsequent infusions may be given over 60 minutes. The default time on Aria is 120 minutes.
- If the patient experiences early symptoms or signs of infusion reaction immediately discontinue the infusion and administer appropriate treatment with chlorpheniramine and hydrocortisone. Once the patient has fully re-covered the infusion may be restarted slowly by infusing 5% of the total dose over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.
- Doxorubicin pegylated liposomal is incompatible with sodium chloride 0.9%. Always use a glucose 5% flush.
- Do not use in-line filters during the administration of doxorubicin pegylated liposomal.

- Doses of doxorubicin pegylated liposomal less than 90mg may be diluted in 250ml of glucose 5%. Doses of 90mg and above should be diluted in 500ml of glucose 5%.

Additional Therapy

- Antiemetics

  15 – 30 minutes prior to chemotherapy

  - dexamethasone 8mg oral or intravenous
  - 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
  - ondansetron 8mg oral twice a day for 3 days

- Mouthwashes for the treatment and prevention of mucositis or stomatitis as per local policy.

- 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.

- For patients experiencing infusion reactions with this regimen consider administering premedication with all subsequent cycles:

  - chlorphenamine 10mg intravenous
  - dexamethasone 20mg intravenous (remove anti-emetic dose)
  - ranitidine 50mg intravenous

References

1.Pujade-Lauraine E, Mahner S, Kaern J, et al. A randomized, phase III study of Carboplatin and pegylated liposomal doxorubicin versus carboplatin and paclitaxel in relapsed platinum sensitive ovarian cancer (OC): CALYPSO study of the Gynecologic Cancer Intergroup (GCIG). J Clin Oncol 2009; 27:18s, (suppl; abstr LBA5509)

REGIMEN SUMMARY

Carboplatin (AUC5)- Doxorubicin pegylated liposomal (Caelyx)

Day 1

1. Dexamethasone 8mg oral or intravenous
   Administration Instructions
   Administer dexamethasone 8mg (or equivalent dose) intravenous if the oral route is not appropriate

2. Ondansetron 8mg oral or intravenous
   Administration Instructions
   Administer ondansetron 8mg intravenous if the oral route is not appropriate

3. Doxorubicin pegylated liposomal 30mg/m^2 intravenous infusion in 250ml glucose 5% over 120 minutes.

4. 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.

5. Carboplatin AUC 5 intravenous infusion in 500ml glucose 5% over 60 minutes
   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

Take Home Medicines

6. Dexamethasone 4mg oral twice a day for 3 days starting on day 2 of the cycle
   Administration Instructions
   Take 4mg twice a day (morning and lunch) for 3 days starting on day 2 of the cycle

7. 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

8. Ondansetron 8mg oral twice a day for 3 days starting on the evening of day 1 of the cycle
   Administration Instructions
   Administer 8mg twice a day starting on the evening of day 1 of the cycle

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.3	May 2023	Name of Liposomal Doxorubicin updated to doxorubicin pegylated liposomal	Alexandra Pritchard Pharmacist	Tom Hurst Pharmacy Technician
1.2	Aug 2022	Carboplatin max dose added Carboplatin national dose bands Coding removed Warning added Administration instructions in summary updated	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	April 2014	Carboplatin maximum dose added Bolus removed from intravenous bolus Metoclopramide dose changed Disclaimer updated Antiemetic start clarified	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	May 2013	None	Rebecca Wills Pharmacist Dr Deborah Wright Pharmacist	Dr Clare Green Consultant Medical Oncologist Dr Cheng Yeoh Consultant Medical 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 Hospital 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.