Chemotherapy Protocol

GYNAECOLOGICAL CANCER

BEVACIZUMAB (15)-CARBOPLATIN (AUC5)-PACLITAXEL (21 day)

Regimen

- Cervix-Bevacizumab (15)-Carboplatin (AUC5)-Paclitaxel (21 day)

Indication

- The first line treatment of recurrent or metastatic stage IVB cervical cancer not amenable to curative treatment with surgery and / or radiotherapy and where there has been no prior treatment with bevacizumab or other anti-VEGF therapy.

- WHO performance status 0, 1

Toxicity

Drug	Adverse Effect
Bevacizumab	Haemorrhage, hypertension, proteinuria, impaired wound healing, gastrointestinal perforations, fistulae, arterial thrombosis
Carboplatin	Thrombocytopenia, peripheral neuropathy, nephrotoxicity at high doses, electrolyte disturbances
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 each cycle

- EDTA or calculated creatinine clearance prior to each cycle

- CA125 prior to each cycle

- Blood pressure and dipstick urinalysis for proteinuria prior to treatment with bevacizumab

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 $1x10^9$/L
Platelets	equal to or more than $100x10^9$/L

Day 1

Neutrophils ($x10^9$/L)	Dose Modifications (carboplatin and paclitaxel)
1 or greater	100%
less than 1	Delay for 7 days. If the counts recover to at least $1x10^9$/L within this time continue with the full dose. If the counts do not recover within 7 days or repeated delays are required then delay until recovery then reduce the dose by 20%
Platelets ($x10^9$/L)	**Dose Modifications (carboplatin and paclitaxel)**
100 or greater	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 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%

There is little need to adjust the dose of bevacizumab for haematological toxicity.

Hepatic Impairment

Drug	Bilirubin (µmol/L)		AST/ALT units	Dose
Bevacizumab	N/A		N/A	No information available
Carboplatin	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
Bevacizumab	N/A	No information available
Carboplatin	less than 20	Omit
Paclitaxel	N/A	No dose adjustment needed

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.

Bevacizumab

Bevacizumab doses should be omitted and not reduced for adverse reactions. If more than two doses are missed due to adverse events treatment should be stopped. It should be noted that the half life of bevacizumab is approximately twenty days. Discontinuation of treatment in response to adverse effects is not expected to influence the short term clinical evolution of the event, symptomatic treatment is often necessary.

Bevacizumab should be stopped if the individual develops;

- Gastrointestinal perforation
- Arterial thromboembolic events
- NCI-CTC grade 3 and above haemorrhagic events (requiring a blood transfusion or a major non-elective intervention)
- NCI-CTC grade 3 and above congestive heart failure or left ventricular function
- NCI-CTC grade 4 fistula

If a NCI-CTC symptomatic grade 4 venous thromboembolic event occurs bevacizumab should be stopped. However, if this is a pulmonary embolism bevacizumab may be re-started once a full recovery has been made and the individual is anti-coagulated with a subcutaneous low molecular weight heparin. An oral anticoagulant must not be used. Hypertension is a common consequence of bevacizumab therapy. For a NCI-CTC grade 1 hypertension no treatment is necessary. NCI-CTC grade 2 hypertension, consider anti-hypertensive therapy. For a NCI-CTC grade 3 and above hypertension that is persistent consider stopping treatment.

Bevacizumab may be continued for a NCI-CTC grade 1 proteinuria or the first occurrence of a grade 2 proteinuria. For the second occurrence of a NCI-CTC grade 2 proteinuria or any NCI-CTC grade 3 proteinuria give the bevacizumab as scheduled. A 24 hour urine collection or UPCR should be conducted at most three days before the next dose. If there is less than 2g protein per 24 hours or a UPCR 0-1 administer the bevacizumab and return to dipstick monitoring. If there is more than 2g protein per 24 hours omit the bevacizumab. Repeat the 24 hour urine collection prior to the next scheduled dose. If this is less than 2g per 24 hours administer the bevacizumab and continue 24 hour urine collection until the protein is 1g per 24 hours or less.

Regimen

21 day cycle until disease progression or unacceptable toxicity (six cycles will be set in Aria)

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 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

Cycles 1 - 6

Drug	Dose	Days	Administration
Bevacizumab	15mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)
Carboplatin	AUC 5 (max dose)	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

- Bevacizumab will be dose banded in accordance with the national dose bands (25mg/ml)
- 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.
- Paclitaxel will be dose banded in accordance with the national dose bands (6mg/ml)

Administration Information

Extravasation

- Bevacizumab – neutral
- Carboplatin – irritant
- Paclitaxel - vesicant

Other

- The first infusion of bevacizumab will be over 90 minutes. If this is well tolerated the second infusion may be given over 60 minutes. If this is well tolerated subsequent infusions may be given over 30 minutes
- 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

- Premedication to reduce of risk of hypersensitivity reaction

  30 minutes before paclitaxel

  - 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. Perren TJ, Swart AM, Pfisterer J et al. A phase three trial of bevacizumab in ovarian cancer. N Engl J Med 2011; 365 (26): 2484-2496.
2. Stark D, Nankivell M, Pujade-Lauraine E et al. Standard chemotherapy with or with out bevacizumab in advanced ovarian cancer: quality of life outcomes from the International Collaboration on ovarian neoplasms (ICON 7) phase 3 randomised trial. Lancet Oncology 2013; 14 (3): 236-243.

REGIMEN SUMMARY

Bevacizumab (15)-Carboplatin (AUC5)-Paclitaxel (21 day)

Cycle 1, 2, 3, 4, 5, 6

1. Bevacizumab 15mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes

2. Chlorphenamine 10mg intravenous

3. Dexamethasone 20mg intravenous

4. 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;

   Ranitidine 50mg intravenous once only
   Famotidine 20mg oral once only
   Nizatidine 150mg oral once only
   Ranitidine 150mg oral once only

   If there is no stock of these products due to national shortages treatment may proceed without the H_2 antagonist provided there is no instruction in the ARIA journal indication the patient **must have** H_2 antagonist treatment.

   All infusion related reactions must be recorded in the ARIA journal and reported to the appropriate consultant. 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.

5. Ondansetron 8mg oral or intravenous
   Administration Instructions
   Administration Instructions
   This may be given as ondansetron 8mg intravenous if required

6. Paclitaxel 175mg/m^2 in 500ml sodium chloride 0.9% intravenous infusion over 180 minutes

7. 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.

8. 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

9. Dexamethasone 4mg oral twice a day for 3 days starting the day after chemotherapy
   Administration Instructions
   Take 4mg twice a day for 3 days starting on day 2 of the cycle

10. Metoclopramide 10mg oral three times a day for three days then 10mg three times a day when required for nausea
    Administration Instructions
    Please supply 28x10mg tablets or nearest equivalent pack size

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Aug 2022	Carboplatin changed to national dose bands Warning added to summary Admin instructions added to summary	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	Nov 2020	Update of premedication due to shortage of IV ranitidine. IV ranitidine changed to H_2 antagonist according to local formulary choice and availability Coding removed Dose banding updated	Donna Kimber Pharmacy Technician	Rebecca Wills Pharmacist
1	April 2014	None	Dr Deborah Wright Pharmacist	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.