

Chemotherapy Protocol

GYNAECOLOGICAL CANCER

BEVACIZUMAB (15)-CARBOPLATIN (AUC4)-GEMCITABINE (day 1, 8)

Regimen

- Ovary-Bevacizumab (15)-Carboplatin (AUC4)-Gemcitabine (1, 8)

Indication

- Recurrent platinum sensitive ovarian, peritoneal or fallopian tube cancer
- WHO performance status 0, 1, 2

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
Gemcitabine	Peripheral oedema, diarrhoea, constipation, rash, respiratory problems, influenza like symptoms, radiosensitising

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, please note these haematological dose modifications apply only to cycles 1 to 6 inclusive and not the maintenance bevacizumab. There is little need to adjust the dose of bevacizumab for haematological toxicity.

If dose modifications to gemcitabine dose are required on day 1 continue with this reduced dose on day 8.

Criteria	Eligible Level
Neutrophil	equal to or more than $1 \times 10^9/L$
Platelets	equal to or more than $100 \times 10^9/L$

Day 1

Neutrophils ($\times 10^9/L$)	Dose Modifications (carboplatin and gemcitabine)
1 or greater	100%
less than 1	Delay one week. If, at this point, the counts are $1 \times 10^9/L$ or greater then continue with full dose. If the counts are still less than $1 \times 10^9/L$ delay a further week and if the counts recover at this point continue with 80% dose of both agents. Otherwise consider stopping treatment.
Platelets ($\times 10^9/L$)	Dose Modifications (carboplatin and gemcitabine)
100 or greater	100%
50-99	Delay one week. If, at this point the platelets are $100 \times 10^9/L$ or greater continue with full dose. If the platelets are still less than $100 \times 10^9/L$ then delay a further week. If the counts recover at this point continue with 80% dose of both agents. Otherwise consider stopping treatment.
less than 50	Delay until recovery to $100 \times 10^9/L$ or greater then continue with 50% doses.

Day 8

Neutrophils (x10 ⁹ /L)	Dose Modifications (gemcitabine)
1 or greater	100%
0.5-1.0	80%
less than 0.5	Omit
Platelets (x10 ⁹ /L)	Dose Modifications (gemcitabine)
100 or greater	100%
50-100	80%
less than 50	Omit

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
Gemcitabine	30 or greater	N/A	Initiate treatment at 800mg/m ²

Renal Impairment

Drug	Creatinine Clearance (ml/min)	Dose (% of original dose)
Bevacizumab	n/a	No information available
Carboplatin*	less than 20	Omit
Gemcitabine	less than 30	Consider dose reduction

* 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 80% 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](#)

The starting dose of carboplatin AUC 4 is used with calculated GFR. AUC 3 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 4 is 600mg (creatinine clearance 125ml/min). This is not a dose included in the national dose banding table. The maximum dose has been set at 630mg 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.

21 day cycle for 6 cycles

Drug	Dose	Days	Administration
Bevacizumab	15mg/kg	1	Intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes (see administration information)
Carboplatin	AUC 4 (max dose)	1	Intravenous infusion in 500ml Glucose 5% over 60 minutes
Gemcitabine	1000mg/m ²	1, 8	Intravenous infusion in 250ml sodium chloride 0.9% over 30 minutes

Followed by;

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

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

[Dose Information](#)

- Bevacizumab will be dose banded in accordance with the national dose bands
- For elderly/frail patients or those with poor performance status consider using carboplatin AUC 3 and/or gemcitabine 750mg/m²
- The recommended maximum dose when using a calculated creatinine clearance at AUC4 is 600mg. This will be set at 630mg to comply with national dose bands. 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 dose will be dose banded in accordance with the national dose bands (10mg/ml)

- Gemcitabine will be dose banded in accordance with the national dose bands (38mg/ml)

Administration Information

Extravasation

- Bevacizumab – neutral
- Carboplatin – irritant
- Gemcitabine – neutral

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

Additional Therapy

- Antiemetics

15-30 minutes prior to chemotherapy on day 1

- dexamethasone 8mg oral or intravenous
- ondansetron 8mg oral or intravenous

As take home medication on day 1

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

15-30 minutes prior to chemotherapy on day 8

- metoclopramide 10mg oral or intravenous

- Gastric protection with a proton pump inhibitor or a H₂ antagonist may be considered in patients considered at high risk of GI ulceration or bleed.

References

1. Aghajanian C, Blank SV, Goff BA et al. OCEANS: A randomized double blind placebo controlled phase III trial of chemotherapy with or without bevacizumab in patients with platinum sensitive recurrent epithelial, ovarian, primary peritoneal or fallopian tube cancer. J Clin Oncol 2012; 30 (17): 2039-2045.

REGIMEN SUMMARY

Bevacizumab (15)-Carboplatin (AUC4)-Gemcitabine (1, 8)

Cycles 1, 2, 3, 4, 5, 6

Day 1

1. Bevacizumab 15mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes
2. Dexamethasone 8mg oral or intravenous
Administration Instructions
This may be given as dexamethasone 8mg intravenous if required
3. Ondansetron 8mg oral or intravenous
Administration Instructions
This may be given as ondansetron 8mg intravenous if required
4. Gemcitabine 1000mg/m² in 250ml sodium chloride 0.9% intravenous infusion over 30 minutes.
5. 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 4 is 600mg. The national dose bands do not contain this dose so the cap has been set at 630mg in ARIA. Please check this dose is appropriate for your patient.
6. Carboplatin AUC 4 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 4 is 600mg. The national dose bands do not contain this dose so the cap has been set at mg in ARIA. Please check this dose is appropriate for your patient

Take Home Medicines (day 1 only)

7. Dexamethasone 4mg oral twice a day for 3 days starting on day 2 of the cycle
Administration Instructions
Take 4mg twice a day for 3 days starting on day 2 of the cycle
8. 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.

Day 8

9. Metoclopramide 10mg oral or intravenous
Administration Instructions
May be give as metoclopramide 10mg intravenous if required
10. Gemcitabine 1000mg/m² in 250ml sodium chloride 0.9% intravenous infusion over 30 minutes.

Cycle 7, 8, 9, 10, 11

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

Cycle 12

12. Warning – Check further cycles required
13. Bevacizumab 15mg/kg intravenous infusion in 100ml sodium chloride 0.9% over 90 minutes

DOCUMENT CONTROL

Version	Date	Amendment	Written By	Approved By
1.2	Aug 2022	Carboplatin changed to national dose bands Warning added in summary Administration instructions added in summary Coding removed	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1.1	March 2014	Name changed to include bevacizumab dose Carboplatin maximum dose added under regimen Intravenous bolus changed to bolus Metoclopramide dose changed to 10mg OPCS updated Disclaimer updated	Dr Deborah Wright Pharmacist	Donna Kimber Pharmacy Technician
1	July 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.