## DRUG ADMINISTRATION

<table>
<thead>
<tr>
<th>Day</th>
<th>Drug</th>
<th>Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1</td>
<td>Bevacizumab</td>
<td>15mg/kg</td>
<td>Infusion</td>
<td>100mls 0.9% Sodium Chloride 90mins, then 60mins then 30min</td>
</tr>
<tr>
<td>Day 1</td>
<td>Sodium Chloride 0.9%</td>
<td>250/500ml</td>
<td>Infusion</td>
<td>Fast Running</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>8mg</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral /Slow bolus/15 min infusion</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>AUC 4 to5</td>
<td>IV Infusion</td>
<td>500/250ml 5% Glucose over 30 to 60 Minutes</td>
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<tr>
<td></td>
<td>Gemcitabine</td>
<td>1000mg/m²</td>
<td>Intravenous</td>
<td>250ml 0.9% Sodium Chloride over 30minutes</td>
</tr>
<tr>
<td>Day 8</td>
<td>Sodium Chloride 0.9%</td>
<td>250/500ml</td>
<td>Infusion</td>
<td>Fast Running</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
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Check correct protocol is being use; there are three similar gynaecological cancers protocols with different Bevacizumab doses.
- 7.5mg/kg is used for 1st line ovarian with carboplatin paclitaxel.
- 15mg/kg is used for 2nd line ovarian with carboplatin gemcitabine
- 15mg/kg is used for cervical cancer with carboplatin paclitaxel.

## DOSE FREQUENCY

Every 21 days for the first six cycles and then continue with bevacizumab alone until disease progression or toxicity.

## RATE

Bevacizumab must be given in combination with chemotherapy every three weekly. Intravenous infusion given over 90 minutes for initial dose; if tolerated next infusion can be given over 60 minutes; can thereafter be given over 30 minutes. It can be given in 100ml Sodium Chloride provided the final solution stays within the range of 1.4-16.5 mg/ml.

## EXCLUSION CRITERIA

Contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies

Caution in patients with:
- Untreated central nervous system metastases
- Uncontrolled hypertension
- History/ Risk factors for thromboembolic events e.g. history of arterial thromboembolic events
- Significant cardiac risk factors for development of CHF
- Patients with baseline renal function less than 30ml/min (Creatinine Clearance)
APPROVED INDICATIONS

Approved for use on the National Cancer drugs Fund List for the second line treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer where all the following criteria are met:

1. Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
2. 2nd line indication
3. Platinum sensitive epithelial ovarian, fallopian tube or primary peritoneal cancer (6 or more months after completion of first line chemotherapy)
4. Given with Carboplatin and Gemcitabine combination chemotherapy
5. PS 0 or 1
6. No previous treatment with bevacizumab or other anti-VEGF treatment
7. Bevacizumab dose to be 15mg/kg every 3 weeks
8. Note: Bevacizumab should be discontinued due to toxicity or disease progression, which ever occurs first. in ovarian cancer it must be used within the Trust’s governance framework.

No treatment breaks of more than 7 weeks are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes.

PREMEDICATION

• Anti-emetics are not required for Bevacizumab treatment.
• Take home medications as per chemotherapy regimen.

RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2 to 3 days
Dexamethasone 4mg twice daily for 1 to 3 days
Metoclopramide 10mg three times daily as required
Loperamide as required (4mg after first loose stool and 2mgs every 2 hours, to a maximum of 16 (2mg) tablets in 24 hours.

INVESTIGATIONS / MONITORING REQUIRED

Pre treatment:
• Assessment of renal function, FBC, Cardiac history
• Cardiac assessment incl. history and physical exam
• Check renal function before commencing platinum. Use EDTA or Wright formulae to calculate GFR

Prior to each cycle
• FBC, U&E’s, LFT’s as required; GFR doubled checked using Wright formulae
• Tumour markers as appropriate, e.g. where CEA is elevated this should be measured before each cycle
Monitor blood pressure every cycle and more frequently in patients who develop hypertension.

Proteinuria by dipstick analysis prior to treatment and before each dose. If protein present undertake quantitative measurement of protein in urine and if greater than 2g > 24hrs delay of bevacizumab.

ASSESSMENT OF RESPONSE
Assessed radiologically after each cycle.
Metastatic: Tumour size and patient symptomatic response

REVIEW BY CLINICIAN
Review at each cycle as appropriate

NURSE / PHARMACIST LED REVIEW
Each cycle as applicable according to local protocols

ADMINISTRATION NOTES

BEVACIZUMAB

- Hypertension is commonly observed, may be dose-related and should be managed with antihypertensives, e.g. calcium channel blockers.
- Units administering bevacizumab must have facilities available for the treatment of anaphylaxis and resuscitation.
- May not need to stop treatment for minor hypersensitivity e.g. reactions, flushing, localised rash. Must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.
- Paracetamol can be used to treat reactions.
- Bevacizumab therapy should not be initiated for at least 28 – 60 days following major surgery or until the surgical wound is fully healed. If elective surgery is planned, bevacizumab should be withheld and the long half-life considered.

CARBOPLATIN AND GEMCITABINE

- May not need to stop treatment for minor hypersensitivity e.g. reactions, flushing, localised rash. Must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.
- If patient has hypersensitivity reaction follow manufacturers re-challenge guidelines before continuing with treatment.

No treatment breaks of more than 7 weeks from the start of the previous cycle are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes.

EXTRAVASATION Follow Network and Local Trust Guidelines
SECOND LINE OVARIAN BEVACIZUMAB (AVASTIN®),
CARBOPLATIN & GEMCITABINE PROTOCOL
Cumbria, Northumberland, Tyne & Wear Area Team

MAIN TOXICITIES

CARBOPLATIN AND PACLITAXEL
- Risk of hypersensitivity and anaphylaxis, particularly when used second-line, start within a few minutes of administration
- Nausea and vomiting
- Myelosuppression, particularly, thrombocytopenia, anaemia & neutropenia
- Nephrotoxicity
- Peripheral neuropathy
- Otological impairment, especially at 8000 Hz
- Haematuria
- Dizziness during infusion
- Oedema/peripheral oedema
- Rarely pulmonary effects e.g. ARDS Lethargy
- Mild Alopecia

BEVACIZUMAB
- Fatigue Hypertension Proteinuria Headache
- Infusion-associated symptoms / acute hypersensitivity reactions (anaphylaxis, chills and fever, nausea, vomiting, pain, rigors, headache, asthenia etc.)
- Diarrhoea
- Abdominal pain
- Nausea and vomiting

Less Common Toxicities that may be severe or life-threatening include:
- Arterial/venous thromboembolism
- GI perforation, fistulas, wound dehiscence
- Haemorrhage
- Cardiac failure
- Pneumonitis

DOSE MODIFICATIONS

Haematological toxicity:

Proceed On Day 1 If:-

| WCC ≥ 3.0 | PLT ≥ 100 | ANC ≥ 1.5 |

Delay 1 week on DAY 1 if:-

| WCC < 3.0 | PLT <100 | ANC <1.5 |

- If Hb < 10 & patient symptomatic will need blood transfusion, but may proceed with chemotherapy as planned if performance status (PS) stable.
- If pre-treatment U&E’s & LFT’s abnormal, delay treatment 1 week and discuss with Oncologist as may need dose reduction.
SECOND LINE OVARIAN BEVACIZUMAB (AVASTIN®),
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Non-Haematological Toxicity:-
- If PS deteriorates to 3 or 4 and on assessment patient is more symptomatic\nwithhold treatment and discuss with Oncologist

Bevacizumab dose reduction for toxicity is not recommended, but dosing with bevacizumab should be omitted or discontinued for the following adverse events: Uncontrollable hypertension, delayed wound healing, surgery, grade 3 proteinuria (>3g in 24hrs ref. CTCv4).

When receiving in combination with chemotherapy, if a cycle of chemotherapy is delayed for any reason, the bevacizumab dose should also be delayed until the patient is fit enough for chemotherapy

HYPERTENSION
Baseline blood pressure should be < 150/100mmHg
A suggested assessment of blood pressure results is:
If diastolic increase > 20mmHg above baseline or blood pressure rises to > 150/100mmHg, antihypertensive therapy may be required. Treatment, and initial monitoring until stabilised, is usually best managed via the patient’s GP.
If blood pressure > 180/110mmHg, it is advised that bevacizumab therapy is withheld until blood pressure controlled.

PROTEINURIA
A suggested assessment of urine dipstick results is:
1+ or 2+ on dipstick (0.3-2.9g/L): continue with bevacizumab. (No additional evaluation required).
3+ on dipstick (3-19g/L): May have dose of bevacizumab as scheduled, but will need 24 hour urine to measure 24 hour protein to be done a few days before next cycle due.
If 24hour protein result < 2g, continue with bevacizumab, continued with proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein level falls to <1g/24hr, return to dipstick analysis.
If ≥ 2g, withhold bevacizumab until repeat 24 hour urine collection shows <2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24 hour urine.
4+ on dipstick (≥20g/L): withhold bevacizumab. 24 hour urine required. Follow 24 hour urine monitoring and guidance as for 3+ on dipstick.

RENAI IMPAIRMENT
There are no data for bevacizumab in patients with impaired renal function. However, dose adjustments would not be expected to be required.

HEPATIC IMPAIRMENT
There are no data for bevacizumab in patients with impaired liver function. However, dose adjustments would not be expected to be required.

TREATMENT LOCATION
Can be given at Cancer Centre or Cancer Unit
REFERENCES


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<tr>
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<td>Mandy Nagra</td>
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