CERVICAL CANCER BEVACIZUMAB (AVASTIN®),
CARBOPLATIN & PACLITAXEL PROTOCOL
Cumbria, Northumberland, Tyne & Wear Area Team

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>20mg</td>
<td>Intravenous</td>
<td>In 50ml NaCl 0.9% over 15 minutes</td>
</tr>
<tr>
<td></td>
<td>Chlorphenamine</td>
<td>10mg</td>
<td>Intravenous</td>
<td>Slow bolus</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td>50mg</td>
<td>Intravenous</td>
<td>50ml NaCl 0.9% over 20 minutes</td>
</tr>
<tr>
<td></td>
<td>Ondansetron*</td>
<td>8mg</td>
<td>Oral/IV</td>
<td>Slow bolus or 15 min infusion (patients over 65 years)</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>175mg/m²</td>
<td>IV Infusion</td>
<td>500ml NaCl 0.9% over 3hrs (Use PVC Free Bag &amp; Line) (start infusion very slowly)</td>
</tr>
<tr>
<td></td>
<td>Carboplatin</td>
<td>AUC 5 or 6</td>
<td>IV Infusion</td>
<td>500/250ml 5% Glucose over 30 to 60 Minutes</td>
</tr>
</tbody>
</table>

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 use for 2nd line ovarian with carboplatin gemcitabine
- 15mg/kg is used for cervical cancer with carboplatin paclitaxel.

DOSE FREQUENCY
Every 21 days until toxicity or disease progression

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 Drug Fund for the first line treatment of recurrent or metastatic cervical cancer in combination with chemotherapy

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. Histologically confirmed carcinoma of the cervix
3. Indication for 1st line palliative chemotherapy
4. Primary stage IVB, recurrent, or persistent disease not amenable to curative treatment with surgery and/or radiotherapy.
5. Given with Paclitaxel and either Cisplatin or Carboplatin
6. PS 0 or 1
7. No previous treatment with bevacizumab or other anti-VEGF therapy
8. No contra-indication to the use of bevacizumab
9. Bevacizumab dose to be 15mg/kg every 3 weeks

Note: Bevacizumab is ONLY approved for use in combination with combination chemotherapy and is not approved for use as a single agent maintenance therapy

Note: Bevacizumab should be discontinued due to toxicity or disease progression, whichever occurs first.

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.
- Premedication of dexamethasone, ranitidine and chlorphenamine is given prior to Paclitaxel infusion to reduce of risk of hypersensitivity reaction. Dexamethasone can be given either as 20mg orally 12 and 6 hours prior to treatment or a 20mg IV bolus prior to treatment

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 PACLITAXEL
- Paclitaxel must be administered via a non-PVC administration set
- There is a risk of infusion reactions with paclitaxel. This is commonly with the first two cycles and often within the first few minutes of starting chemotherapy.
- 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.
- Units administering paclitaxel must have facilities available for the treatment of anaphylaxis and resuscitation.
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- Blood pressure & pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion

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

MAIN TOXICITIES

CARBOPLATIN AND PACLITAXEL
- Risk of hypersensitivity and anaphylaxis, particularly on first and second cycle, start within a few minutes of administration
- Nausea and vomiting
- Hypotension and bradycardia
- Myelosuppression, particularly, thrombocytopenia, anaemia & neutropenia
- Nephrotoxicity
- Alopecia
- Peripheral neuropathy
- Otological impairment, especially at 8000 Hz
- Myalgia
- Back pain on administration

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:-

<table>
<thead>
<tr>
<th>WCC ≥ 3.0</th>
<th>PLT ≥ 100</th>
<th>ANC ≥ 1.5</th>
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Delay 1 week on DAY 1 if:-

<table>
<thead>
<tr>
<th>WCC &lt; 3.0</th>
<th>PLT &lt; 100</th>
<th>ANC &lt; 1.5</th>
</tr>
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</table>

- 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.

Non-Haematological Toxicity:-

- If PS deteriorates to 3 or 4 and on assessment patient is more symptomatic withhold 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 24 hour 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 reintroduce 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.
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RENAL 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