BEVACIZUMAB (AVASTIN®), CARBOPLATIN & PACLITAXEL
for Cervical Cancer

DRUG ADMINISTRATION SCHEDULE

<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></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>See Below*</td>
<td></td>
<td></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 mins</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>Day 1</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>
<tr>
<td></td>
<td>Sodium Chloride 0.9%</td>
<td></td>
<td>Line should be flushed with 0.9% NaCl prior to administration of bevacizumab</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Bevacizumab</td>
<td>15 mg/kg</td>
<td>Infusion</td>
<td>100mls 0.9% Sodium Chloride See below for rate</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 used for cervical cancer with carboplatin paclitaxel.

DOSE FREQUENCY
Every 21 days for the first six cycles

BEVACIZUMAB RATE
Bevacizumab must be given in combination with chemotherapy every three weeks. 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.

APPROVED INDICATIONS
The first line treatment of recurrent or metastatic cervical cancer in combination with chemotherapy 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. 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. ECOG 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 for reasons of toxicity or disease progression, whichever occurs first

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 (congestive heart failure)
- Patients with baseline renal function less than 30ml/min (Creatinine Clearance)

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 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

Antiemetic cover with neurokinin 1 (NK1) receptor antagonists
ASCO 2017 antiemetic guidance recommends regimens containing carboplatin ≥ AUC4 should be classified as high risk of CINV and patients offered a three-drug combination of a neurokinin 1 (NK1) receptor antagonist, a serotonin (5-HT3) receptor antagonist and dexamethasone. Current practice in NCA is to start with a two-drug regimen serotonin (5-HT3) receptor antagonist and dexamethasone and add in a neurokinin 1 (NK1) receptor antagonist if CINV not adequately controlled. However, if pre-assessment of patient identifies risk factors for CINV, units may wish to start with a 3-drug combination.

RECOMMENDED TAKE HOME MEDICATION
Ondansetron 8mg twice daily for 2 to 3 days
Dexamethasone 4mg twice daily for 1 to 3 days and as above if oral pre-medication used
Metoclopramide 10mg three times daily as required

Suggested antiemetic regimen - may vary with local practice. See CINV policy for more details

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&Es, LFTs 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.

PACLITAXEL
- Paclitaxel must be administered via a non-PVC administration set and 0.2-micron filter.
- 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.
- Blood pressure & pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.
CARBOPLATIN
- Patient needs Glomerular Filtration Rate (GFR) prior to commencement of treatment for calculation of Carboplatin dosage. Subsequent measurement of GFR only needed if serum creatinine changes by >20% from initial measurement.
- 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.

EXTRAVASATION Follow NCA 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:

| PLT ≥ 100 | ANC ≥ 1.0 |

Delay 1 week on DAY 1 if:

| PLT <100  | ANC <1.0  |
Bevacizumab (Avastin®), Carboplatin & Paclitaxel for Cervical Cancer

- 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&Es & LFTs 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.
If diastolic increase > 20mmHg above baseline or blood pressure rises to > 150/100mmHg, antihypertensive therapy may be indicated. 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:

<table>
<thead>
<tr>
<th>1+ or 2+ on dipstick (0.3-2.9g/L)</th>
<th>Continue with bevacizumab (no additional evaluation required).</th>
</tr>
</thead>
<tbody>
<tr>
<td>3+ on dipstick (3-19g/L)</td>
<td>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.</td>
</tr>
<tr>
<td></td>
<td>• If 24-hour protein result &lt; 2g, continue with bevacizumab with proteinuria monitoring via 24-hour urine before each dose. If the 24-hour protein level falls to &lt;1g/24hr, return to dipstick analysis.</td>
</tr>
<tr>
<td></td>
<td>• If ≥ 2g, withhold bevacizumab until repeat 24-hour urine collection shows &lt;2g protein. Then re-introduce bevacizumab, with continued proteinuria monitoring via 24-hour urine.</td>
</tr>
<tr>
<td>4+ on dipstick (≥20g/L)</td>
<td>Withhold bevacizumab. 24-hour urine required. Follow 24-hour urine monitoring and guidance as for 3+ on dipstick.</td>
</tr>
</tbody>
</table>

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

Carboplatin - If creatinine level increases by >20% from the result used to calculate GFR (or pre-treatment baseline if EDTA performed) discuss with consultant and consider repeating EDTA.
HEPATIC IMPAIRMENT
There are no data for bevacizumab in patients with impaired liver function. However, dose adjustments would not be expected to be required.

Paclitaxel Dose reduction of 25% in patients with disturbed liver biochemistry. Contraindicated if Bilirubin > x 2.5 ULN, Transaminases > x 2.5 ULN,

TREATMENT LOCATION
Can be given at Cancer Centre or Cancer Unit

REFERENCES
3. Ozols RF et al. Phase III trial of carboplatin and paclitaxel compared with cisplatin and paclitaxel in patients with optimally resected stage III ovarian cancer:
4. Kristensen et al; JCO 2011; 29 suppl; abstract LBA5006 (ICON 7)