Bevacizumab (Avastin®) & Paclitaxel– The treatment of Advanced Breast Cancer

DRUG ADMINISTRATION

<table>
<thead>
<tr>
<th>Da</th>
<th>Drug</th>
<th>Daily Dose</th>
<th>Route</th>
<th>Diluent &amp; Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 1,15</td>
<td>Bevacizumab</td>
<td>10 mg/kg</td>
<td>Infusion</td>
<td>250mls Sodium Chloride 0.9%*</td>
</tr>
<tr>
<td>Day 1,8,15 &amp; 22</td>
<td>Sodium Chloride 0.9%</td>
<td>100ml</td>
<td>Infusion</td>
<td>Fast Running</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral</td>
<td>Via saline drip</td>
</tr>
<tr>
<td></td>
<td>Chlorphenamine</td>
<td>10 mg</td>
<td>Iv bolus</td>
<td>Via saline drip</td>
</tr>
<tr>
<td></td>
<td>Ranitidine</td>
<td>50 mg</td>
<td>Iv bolus</td>
<td>Via saline drip</td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>10 mg*</td>
<td>Iv bolus</td>
<td>Via saline drip</td>
</tr>
<tr>
<td></td>
<td>Paclitaxel</td>
<td>90 mg/m²</td>
<td>Infusion</td>
<td>250mls 5% Glucose or 0.9% Sodium Chloride 1 hour</td>
</tr>
</tbody>
</table>

CYCLE LENGTH AND NUMBER OF DAYS

28 day cycle until disease progression

RATE

Bevacizumab 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

If a patient experiences a mild infusion-related reaction, give future doses with pre medication cover of paracetamol 100mg and chlorphenamine IV 10mg. If the patient still experiences an infusion-related reaction, consider increasing the infusion time back up to 60 minutes or 90 minutes, as appropriate.

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 tromboembolic events
- Significant cardiac risk factors for development of CHF
ELIGIABILITY CRITERIA

Approved for use on the National Cancer drugs Fund List for patients who meet the following criteria:

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. Advanced breast cancer
3. Triple negative disease (ER, PR and HER2 negative)
4. A) 1st line indication
   B) 2nd line indication
5. To be given in combination with paclitaxel

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

No treatment breaks of more than 8 weeks are allowed. Should treatment breaks be required, then an Individual Funding Request must be submitted as per CDF processes.

PREMEDICATION

Premedication of dexamethasone, ranitidine (or cimetidine) and chlorphenamine is given prior to paclitaxel infusion to reduce of risk of hypersensitivity reaction.

Dexamethasone should be given as a 10mg IV bolus prior to treatment.
*Note lower doses, 8mg or 4mg of dexamethasone can be given after first two cycles if there is concern over the effect of cumulative doses of steroids.

RECOMMENDED TAKE HOME MEDICATION

Metoclopramide 10 to 20mgs three to four times daily as required

INVESTIGATIONS / MONITORING REQUIRED

Pre Treatment:
- Assessment of renal function, FBC, Cardiac history
- Cardiac assessment incl. history and physical exam
Prior to each cycle
- FBC, U&E’s, LFT’s
- Tumour markers as appropriate, e.g. where CEA is elevated this should be measured before each cycle
- BP and pulse to be monitored half hourly during paclitaxel infusion
- Monitor blood pressure every 2-3 weeks 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
Metastatic: tumour size and patient symptomatic response

ADMINISTRATION NOTES

• Hypertension is commonly observed, may be dose-related and should be managed with antihypertensives, e.g. calcium channel blockers.
• Units administering paclitaxel and 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 may adversely affect the wound healing process. Therapy should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. For minor surgery, including port placement, it is recommended that bevacizumab is withheld for 7 days after surgery.

EXTRAVASATION See NECN/ Local Policy
Paclitaxel is a vesicant; therefore extreme care must be taken when infusion pumps are used to control rate of administration.

TOXICITIES

• Fatigue
• Hypertension
• Proteinuria
• Headache
• Infusion-associated symptoms / acute hypersensitivity reactions (anaphylaxis, chills and fever, nausea, vomiting, pain, rigors, headache, asthenia etc.)
• Diarrhoea
• Peripheral neuropathy
• Nausea and vomiting
• Myalgia and arthralgia
• Myelosuppression

Less Common Toxicities that may be severe or life-threatening include
• Arterial/venous thromboembolism
• GI perforation, fistulas, wound dehiscence
• Haemorrhage
• RPLS
• Cardiac failure
• Pneumonitis
DOSE MODIFICATION / TREATMENT DELAYS

Haematological Toxicity:
- Delay 1 week if WBC<3.0, ANC <1.0 Platelets <100 week 1
- Week 2 onwards ANC >1.0 and plts >75
- No dose modification for CTC grade I/II ANC
- Grade III/IV ANC → delay chemotherapy until recovered. On recovery give 20% dose reduction
- Note: In the case of asymptomatic dose delay of chemotherapy for haematological toxicity the bevacizumab may still be given if the clinician decides it is appropriate as bevacizumab does not cause significant haematological toxicity.

Non haematological toxicity:
If PS deteriorates to Grade 3 or 4 and/or 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.

Renal and Hepatic dysfunction
No information on dose adjustment. The kidneys and liver are not major organs for bevacizumab metabolism or excretion.

Hypertension:
- Baseline bp should be < 150/100mmHg before bevacizumab is initiated. A suggested assessment of blood pressure results is:
  - If diastolic increase > 200mmHg above baseline or blood pressure rises to > 150/1000mmHg, antihypertensive therapy may be required.
  - If blood pressure > 180/110mmHg, it is advised that bevacizumab therapy is withheld until blood pressure is controlled.

Neuropathy
If grade 1-2 peripheral neuropathy develops, seek advice from consultant regarding: paclitaxel dose reduction

Myalgia/ Arthralgia
Due to Paclitaxel and often co-exist, usually Grade 1 or Grade 2. Management consists of reassuring patients that it is self-limiting. Consider prescribing NSAIDs, but may be ineffective.
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 bevacizumab dose as scheduled, but will need 24 hour urine, a few days before next cycle due, to measure 24 hour protein:
If 24 hour protein result <2g, continue with bevacizumab, with combined proteinuria monitoring via 24 hour urine before each dose. If the 24 hour protein falls to < 1g/24hr, return to dipstick analysis.
If ≥ 2g, withhold bevacizumab until repeat 24 hour urine 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.

TREATMENT LOCATION
Can be given at Cancer Centre or Cancer Unit

REVIEW BY CLINICIAN
To be reviewed by a nurse, a pharmacist or a clinician before every cycle.

NURSE / PHARMACIST LED REVIEW
On cycles where not seen by clinician.

REFERENCES
- Avastin® (bevacizumab). Product Monograph: Roche: Available at Medicines.org.uk