BEVACIZUMAB in Breast cancer

Indication: First line treatment of metastatic breast carcinoma with either Triple-negative tumour and/ or post prior taxane therapy.

Bevacizumab in combination with Paclitaxel chemotherapy (refer to separate protocol for Paclitaxel 90mg/m²)

LCNDG criteria to be met:
- Histologically or cytologically confirmed metastatic breast cancer
- No previous systemic chemotherapy for metastatic disease (except hormones)
- ER, PR and HER2 negative and/or previously treated with taxane in the adjuvant setting, with a disease free interval of at least 12 months after completion of taxane therapy
- ECOG performance status less than or equal to 1

Cancer drug fund application and approval is required for funding.

Drugs/ Dosage: Bevacizumab *10mg/kg IVI 2 weekly; days 1 and 15
(Paclitaxel 90mg/m² IVI weekly; days 1, 8 and 15)

Continue Bevacizumab treatment until progression

*Dose reductions for Bevacizumab are not recommended. If indicated, therapy should either be permanently discontinued or temporarily suspended.

Administration: The initial dose should be delivered over 90 minutes as an intravenous infusion. If the first infusion is well tolerated, the second infusion may be administered over 60 minutes. If the 60-minute infusion is well tolerated, all subsequent infusions may be administered over 30 minutes.

Bevacizumab can be administered before or after combination chemotherapy.

Bevacizumab infusions should not be administered or mixed with glucose solutions. If Bevacizumab is administered following other chemotherapy, flush the line thoroughly with saline solution before starting the infusion.

Availability of resuscitation equipment must be ensured as a standard precaution. Patients should be observed during the infusion for symptoms like fever and chills or other infusion-related symptoms (dyspnoea, flushing, heart rate, blood pressure, temperature, respiration rate, chest pain).

If a patient experiences a mild infusion-related reaction, give future doses with pre-medications cover of paracetamol orally 1000mg and IV chlorphenamine 10mg. If the same patient still experiences an infusion-related reaction, consider increasing the infusion back up to 60 minutes or 90 minutes, as appropriate.

For severe reactions, discuss with consultant before continuing with further treatment.

Frequency: 28 day cycle (D1 & D15), until progression
Toxicities: GI symptoms (see below), GI perforation, diarrhoea and abdominal pain, haemorrhage, thromboembolism, hypertension, fatigue, proteinuria, headache, PPE, arthralgia, muscular weakness, infusion related hypersensitivity reactions

Anti-emetics: Low emetogenicity

Supportive medication: Loperamide tablets 4mg stat, then 2mg prn for diarrhoea Routine pre-medication not required.

Extravasation: Non-vesicant

Regular investigations: BP Baseline and regularly during therapy Urinalysis D1 Proteinuria dipstick analysis FBC D1 (when used in combination with paclitaxel chemotherapy) U&Es D1 (when used in combination with paclitaxel chemotherapy) LFTs D1 (when used in combination with paclitaxel chemotherapy) Dental check Baseline, if previous or concomitant IV biphosphonate therapy

N.B. When given as a single agent, it is sufficient to monitor blood results periodically

Toxicities

Gastrointestinal perforations or fistulae

Patients may be at an increased risk for the development of gastrointestinal perforation or fistulae when treated with Bevacizumab. Intra-abdominal inflammatory process may be a risk factor for gastrointestinal perforations in patients with metastatic carcinoma of the colon or rectum, therefore, caution should be exercised when treating these patients. Therapy should be permanently discontinued in patients who develop gastrointestinal perforation.

Permanently discontinue Bevacizumab in patients with TE (tracheoesophageal) fistula or any grade 4 fistula. Limited information is available on the continued use of Bevacizumab in patients with other fistulae. In cases of internal fistula not arising in the GI tract, discontinuation of Bevacizumab should be considered.

Wound healing and Haemorrhage

Bevacizumab may adversely affect the wound healing process and should not be initiated for at least 28 days following major surgery or until the surgical wound is fully healed. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for 6 weeks before elective surgery.

For minor surgery, including port placement, it is recommended that bevacizumab is withheld for 7 days after surgery. Bevacizumab should be discontinued permanently in patients who experience Grade 3 or 4 bleeding during therapy.

Patients with untreated CNS metastases were routinely excluded from clinical trials with Bevacizumab, based on imaging procedures or signs and symptoms. Therefore, the risk of CNS haemorrhage in such patients has not been prospectively evaluated in randomised clinical trials. Patients should be monitored for signs and symptoms of CNS bleeding, and discontinue treatment in cases of intracranial bleeding.
Haematological Toxicity

Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia have been observed in combination with platinum-based therapies.

Hypertension

An increased incidence of hypertension was observed in Bevacizumab treated patients. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent. Pre-existing hypertension should be adequately controlled before starting treatment (usually best managed via the patient’s GP). Monitoring of blood pressure is generally recommended during therapy.

- If previously undiagnosed hypertension is detected, anti-hypertensive therapy should be given until a BP of $<140/90\text{mmHg}$ is achieved, before Bevacizumab is initiated.
- In Grade 4 hypertension (hypertensive crisis) Bevacizumab should be permanently discontinued.

### Blood pressure during therapy

<table>
<thead>
<tr>
<th>Blood pressure</th>
<th>Bevacizumab dose and action</th>
</tr>
</thead>
<tbody>
<tr>
<td>$&lt;160/100\text{mmHg}$</td>
<td>Continue, no additional antihypertensives required</td>
</tr>
<tr>
<td>$160/100-180/100\text{mmHg}$</td>
<td>Continue unless increased cardiovascular risk</td>
</tr>
<tr>
<td>$&gt;180/110\text{mmHg}$</td>
<td>Hypertension referral required if BP remains in these values despite step 3 NICE guidance regarding management of hypertension</td>
</tr>
<tr>
<td>Malignant phase hypertension</td>
<td>Start or increase antihypertensives</td>
</tr>
<tr>
<td>$&gt;180/110\text{mmHg}$</td>
<td>Suspend until BP $&lt;160/100\text{mmHg}$</td>
</tr>
<tr>
<td>Malignant phase hypertension</td>
<td>Refer for specialist</td>
</tr>
<tr>
<td>Malignant phase hypertension</td>
<td>Start or increase antihypertensives</td>
</tr>
<tr>
<td>Malignant phase hypertension</td>
<td>Discontinue permanently</td>
</tr>
<tr>
<td>Malignant phase hypertension</td>
<td>Emergency referral</td>
</tr>
<tr>
<td>Malignant phase hypertension</td>
<td>Parenteral antihypertensive treatment</td>
</tr>
</tbody>
</table>

Reversible posterior leukoencephalopathy syndrome (RPLS)

There have been rare reports of Bevacizumab-treated patients developing signs and symptoms that are consistent with Reversible Posterior Leukoencephalopathy Syndrome (RPLS), a rare neurologic disorder, which can present with the following signs and symptoms among others: seizures, headache, altered mental status, visual disturbance, or cortical blindness, with or without associated hypertension. A diagnosis of RPLS requires confirmation by brain imaging. In patients developing RPLS, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of Bevacizumab. The safety of reinitiating therapy in patients previously experiencing RPLS is not known.
Proteinuria

Patients with a history of hypertension may be at increased risk for the development of proteinuria. There is evidence suggesting that Grade 1 proteinuria may be related to the dose. Monitoring of proteinuria by dipstick urinalysis is recommended prior to starting and during therapy (see below). Patients with a \( \geq 2 \) urine dipstick reading should undergo further assessment (e.g. 24 hour urine collection). Therapy should be permanently discontinued in patients who develop Grade 4 proteinuria (nephrotic syndrome).

A suggested assessment of urine dipstick result is:

- \( 1+ \) or \( 2+ \) on dipstick (0.3-2.9g/L): continue with Bevacizumab.

- \( 3+ \) on dipstick (3-19g/L): dose may be given, but 24 hour urine collection needs to be arranged to measure 24 hour protein within 3 days before next cycle is planned.
  
  - If 24hour protein result is \( < 2g \), continue with Bevacizumab, with continued proteinuria monitoring via 24hour urine before each dose. If the 24hour protein level falls to \( < 1g/24hr \), return to dipstick analysis.
  
  - If \( \geq 2g \), withhold Bevacizumab until repeat 24hr urine collection shows \( < 2g \) protein. The re-introduce Bevacizumab, with continued proteinuria monitoring via 24hr urine.

- \( 4+ \) on dipstick (\( \geq 20g/L \)): Withhold treatment. 24-hour urine required. Follow 24hr urine monitoring and guidance as for \( 3+ \) on dipstick.

Cardiotoxicity/ Arterial and venous thromboembolism

Prior anthracycline exposure and/or prior radiation to the chest wall may be possible risk factors for the development of CHF. Caution should be exercised before initiating Bevacizumab therapy in patients with these risk factors.

In five randomised clinical trials, the incidence of arterial thromboembolic events including cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) and myocardial infarctions (MIs) was higher in patients receiving Bevacizumab in combination with chemotherapy compared to those who received chemotherapy alone. A history of arterial thromboembolic events or age over 65 years was associated with an increased risk of developing arterial thromboembolic events during therapy. Therapy should be permanently discontinued in patients who develop arterial thromboembolic events.

Patients may be at risk of developing venous thromboembolic events, including pulmonary embolism under Bevacizumab treatment. Discontinue therapy in patients with life-threatening (Grade 4) pulmonary embolism, patients with \( \geq 3 \) Grade 3 need to be closely monitored.

Osteonecrosis of the jaw

Cases of Osteonecrosis of the jaw have been reported in cancer patients treated with Bevacizumab, the majority of whom had received prior or concomitant treatment with IV bisphosphonates, for which ONJ is an identified risk. Caution should be exercised when Bevacizumab and IV bisphosphonates are administered simultaneously or sequentially.
Invasive dental procedures are also an identified risk factor. A dental examination and appropriate preventive dentistry should be considered prior to starting the treatment with Bevacizumab. In patients who have previously received or are receiving IV bisphosphonates invasive dental procedures should be avoided, if possible.

**Renal Impairment**

The safety and efficacy have not been studied in patients with renal impairment. Deteriorating organ function may be a sign of disease progression, therefore always discuss with the consultant.

**Hepatic Impairment**

The safety and efficacy have not been studied in patients with hepatic impairment. Deteriorating organ function may be a sign of disease progression, and require cessation of, or change in, treatment, therefore always discuss with the consultant.

**References:**

[www.medicines.org.uk](http://www.medicines.org.uk), accessed April 2012
[www.micromedex.com](http://www.micromedex.com), accessed April 2012
CDF SELCN documentation, April 2012
Gray R. Et al (2009) JCO; 27: 4966-4972
Consultations with Roche, Feb 2011