LONDON CANCER ALLIANCE West and South

Breast Pathway Group – Bevacizumab & Paclitaxel in Advanced Breast Cancer

Indication:

First-line or second-line treatment of triple negative advanced breast cancer

National Cancer Drug Fund criteria:

- Advanced breast cancer
- Triple negative disease (ER, PR and HER2 negative)
- 1st line or 2nd line indication
- To be given in combination with paclitaxel

Ensure funding has been approved prior to starting treatment

Regimen details:

Bevacizumab	10mg/kg	IV	Day 1 & 15
Paclitaxel	90mg/m^2	IV	Day 1, 8 & 15

Administration:

Bevacizumab in 100ml Sodium Chloride 0.9%
The initial dose should be delivered over 90 minutes. If the first infusion is tolerated well, 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 may be administered before or after chemotherapy. Bevacizumab must not come into contact with glucose solutions; flush the line thoroughly with sodium chloride 0.9% before and after the bevacizumab infusion.

Infusion-related hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, dyspnoea and fever or chills following the start of the infusion; the infusion should be slowed down or interrupted and the necessary supportive medication should be administered. Severe reactions such as hypotension and/or bronchospasm or generalised rash/erythema

Version: 1.0 Supersedes: all other versions	Approved by LCA Breast Pathway Chemotherapy Lead: Mark Harries November 2014
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson
Second check by: Laura Cameron	Date prepared: November 2014 Review Date: November 2016

requires immediate discontinuation. Availability of resuscitation equipment must be ensured as a standard precaution.

Paclitaxel in 250ml Sodium Chloride 0.9% or Glucose 5% over 60 minutes. Paclitaxel to be given via non-PVC infusion bag, with a 0.22 micron in-line filter. Paclitaxel must be diluted to a concentration of 0.3-1.2mg.ml to maintain stability in clinical practice

Frequency:

Bevacizumab on Days 1 and 15, every 28 days, until progression or unacceptable toxicity
Paclitaxel on Day 1, 8 and 15, every 28 days for 6 cycles (18 doses)

Pre-medication:

Dexamethasone	*8mg	IV	30 – 60 minutes prior to paclitaxel administration
Chlorphenamine	10mg	IV	30 – 60 minutes prior to paclitaxel administration over at least 1 minute
Ranitidine	50mg	IV	30 – 60 minutes prior to paclitaxel administration over at least 2 minutes

*To minimise steroid side effects, the dose of dexamethasone may be reduced to 4mg if there has been no evidence of hypersensitivity.

Paracetamol / Chlorphenamine / Hydrocortisone can be given for infusion-related reactions such as chills / fever.

Anti- emetics:

Low emetogenicity
Follow Local Anti-emetic Policy

Supportive medication:

Loperamide can be used to manage diarrhoea
Mouthcare as per Local Policy

Extravasation:

Bevacizumab is non-vesicant
Paclitaxel is vesicant
If there is any possibility that extravasation has occurred, contact a senior member of the medical team and follow local protocol for dealing with cytotoxic extravasation to reduce the risk of permanent tissue damage

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Regular investigation:

Prior to cycle 1	
FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
Blood pressure	Day 1 (within 14 days)
Dental check	if previous or concomitant bisphosphonate therapy
Prior to Day and Day 15 (all cycles):	
FBC	Day 8 or 15 (within 48 hours)
Prior to Day 1 (all cycles)	
FBC	Day 1 (within 72 hours)*
LFTs	Day 1 (within 72 hours)*
U&Es	Day 1 (within 72 hours)*
Blood pressure	Prior to each dose
Urinalysis (Proteinuria dipstick)	Prior to each dose

*Note: When bevacizumab is given as a single agent, it is sufficient to monitor blood results every 8 weeks

CT scan	Every 9 to 12 weeks

Toxicities:

Bevacizumab: Infusion related hypersensitivity reactions, hypertension, fatigue, diarrhoea and abdominal pain, proteinuria, GI perforation and fistulae, haemorrhage especially tumour-associated haemorrhage (including epistaxis, haemoptysis, GI, intracranial, pulmonary or vaginal haemorrhage), thromboembolic events, impaired wound healing including necrotising fascitis, headache, arthalgia, muscular weakness, osteonecrosis of the jaw, cardiotoxicity, Posterior Reversible Encephalopathy Syndrome (rare).

Paclitaxel: Anaemia, neutropenia, thrombocytopenia, fatigue, nausea, vomiting, mucositis, diarrhoea, dysgeusia, hypersensitivity reactions (mainly flushing, rash and hypotension), infection, peripheral neuropathy, arthralgia, myalgia, alopecia

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DOSE MODIFICATIONS

Haematological Toxicity

Neutrophils (x 10^9/L)		Platelets (x 10^9/L)	Paclitaxel Dose
≥ 1.5	&	≥ 50	100%
< 1.5	& / or	< 50	Delay for 1 week. Repeat FBC - if recovered to above these levels resume treatment with 100% dose

If neutrophils < 0.5 x 10^9/L for ≥ 7 days, OR
Febrile neutropenia is diagnosed OR
Platelets < 25x 10^9/L,
Paclitaxel dose should be permanently reduced to 80% for subsequent cycles.

Dose reductions for bevacizumab are not recommended and may be continued during periods of reversible, chemotherapy-induced myelosuppression but monitor closely for complications of neutropenia.

Non-haematological Toxicities

Renal Impairment
Bevacizumab - No formal studies have been conducted in renal impairment however dose adjustments are not expected to be required
Paclitaxel - No dose adjustment required. Assess renal function when clinically indicated

Hepatic Impairment
Bevacizumab - No formal studies have been conducted in renal impairment however dose adjustments are not expected to be required

Bilirubin (µmol/L)	Paclitaxel Dose
22 - 26	Give 75 – 80% dose
27 – 51	Give 40 – 45% dose
> 51	Give 30% dose

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Dose modifications for other toxicities as appropriate

Proteinuria

Proteinuria	Action
1+ or 2+ on dipstick (0.3 – 2.9g/l)	Proceed with bevacizumab treatment
3+ on dipstick (3 - 19g/l)	Bevacizumab may be given, but 24 hour urine collection needs to be arranged to measure 24 hour protein prior to subsequent cycle. Treatment may continue if ≤2g/24h with continued monitoring via 24 hour urine prior to each dose. If the 24 hour protein level falls to <1g/24h, return to dipstick analysis.
4+ on dipstick (≥20g/l)	Withhold bevacizumab and order a 24 hour urine collection; treatment may be resumed when ≤2g/24h - follow guidance for 3+ on dipstick
Nephrotic syndrome or thrombotic microangiopathy	Discontinue bevacizumab permanently

Hypertension

Pre-existing hypertension should be adequately controlled (<140/90mmHg) before starting treatment.

Blood pressure during therapy	Action
< 160/100mmHg	Continue bevacizumab
160/100 - 180/100mmHg	Continue bevacizumab unless increased cardiovascular risk Increase anti-hypertensive treatment Referral required if BP remains at these values despite appropriate management
Severe (≥ 180/110mmHg)	Suspend bevacizumab until BP <160/100mmHg Refer to specialist
Uncontrolled hypertension, hypertensive crisis, hypertensive encephalopathy	Discontinuebevacizumab permanently Emergency referral

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PERIPHERAL NEUROPATHY

NCI CTCAE Grade	Sensory Neuropathy	Paclitaxel Dose
1	Paraesthesia (including tingling), but not interfering with function	100% dose
2	Paraesthesia interfering with function, but not interfering with activities of daily living	80% dose
3	Paraesthesia interfering with activities of daily living	Omit paclitaxel
4	Disabling	Discontinue paclitaxel permanently

ARTHRALGIA / MYALGIA
Paclitaxel may cause Grade 1 or 2 Arthralgia or myalgia

NCI CTCAE Grade	Arthralgia/Myalgia	Action
1	Joint and muscle pain, not interfering with function	Consider use of NSAIDs
2	Joint and muscle pain, interfering with function, but not interfering with activities of daily living	Consider use of NSAIDs

Location of regimen: delivery — Outpatient setting.
Availability of resuscitation equipment must be ensured as a standard precaution.

Comments:

<u>Osteonecrosis of the jaw</u>
Cases of osteonecrosis of the jaw (ONJ) 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. A baseline dental check should be considered prior to starting treatment with bevacizumab in these patients. Non-urgent invasive dental procedures should be avoided, if possible whilst on treatment.

<u>Impaired wound healing and haemorrhage</u>
Therapy should be withheld for 6 weeks before elective surgery. Bevacizumab should not be initiated until at least 28 days following major surgery or until the surgical wound is fully healed.

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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.

Necrotising Fasciitis

Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. The condition is usually secondary to wound healing complications, gastrointestinal perforation or fistula formation. Bevacizumab therapy should be discontinued in patients who develop necrotising fasciitis, and appropriate treatment should be promptly initiated.

Arterial and venous thromboembolic events

Caution when treating patients with a history of arterial thromboembolism or age >65 years.
Arterial thromboembolic reactions such as transient ischaemic attack, cerebrovascular accident, myocardial infarction and angina have been reported in patients treated with bevacizumab - treatment should be permanently discontinued.
Bevacizumab should be discontinued for Grade 4 venous thromboembolic events including pulmonary embolism.

Gastrointestinal perforation or fistulae

Patients may be at an increased risk for the development of gastrointestinal perforation or fistulae (GI and non GI sites) when treated with bevacizumab- therapy should be permanently discontinued.

Cardiotoxicity

Patients with pre-existing cardiovascular disease, prior anthracycline exposure and/or prior radiation to the chest wall may be possible risk factors for the development of chronic heart failure.

Posterior Reversible Encephalopathy Syndrome (PRES)

PRES may present with altered mental status, seizures, headache, visual disturbance or cortical blindness, with or without hypertension. A diagnosis of PRES requires confirmation by brain MRI - bevacizumab should be discontinued.

Drug interactions:	No clinically relevant pharmacokinetic interaction of co-administered chemotherapy on Avastin pharmacokinetics has been observed based on the results of a population PK analysis Increased rates of severe neutropenia, febrile neutropenia, or infection with or without severe neutropenia (including some fatalities) have been observed mainly in patients treated with platinum- or taxane-based therapies in the treatment of NSCLC and mBC

Concomitant administration of inducers or inhibitors of cytochrome P450 Isoenzymes (CYP2C8 and 3A4) may alter the pharmacokinetics of Paclitaxel, presenting a theoretical interaction
Clozapine: avoid concomitant use, increased risk of agranulocytosis

References:

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UCLH-Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009

LCA Breast Cancer Clinical Guidelines October 2013

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