Bevacizumab (Avastin®) for the first line treatment of advanced colorectal cancer with FOLFOX

<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>5mg/kg</td>
<td>Infusion</td>
<td>250mls 0.9% Sodium Chloride Rate see below*</td>
</tr>
<tr>
<td></td>
<td>Glucose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Fast Running for Line Flush</td>
</tr>
<tr>
<td></td>
<td>Ondansetron</td>
<td>8mg</td>
<td>Oral</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Dexamethasone</td>
<td>8mg</td>
<td>IV bolus</td>
<td>Via glucose drip</td>
</tr>
<tr>
<td></td>
<td>Calcium Leucovorin (folinic acid)</td>
<td>300mg</td>
<td>Infusion</td>
<td>250ml Glucose 5% over 2 hours concurrent with oxaliplatin</td>
</tr>
<tr>
<td></td>
<td>Oxaliplatin</td>
<td>85 mg/ m²</td>
<td>Iv Infusion</td>
<td>250ml Glucose 5% over 2 hours concurrent with folinic acid</td>
</tr>
<tr>
<td></td>
<td>Glucose 5%</td>
<td>500ml</td>
<td>Infusion</td>
<td>Line Flush</td>
</tr>
<tr>
<td></td>
<td>5 Fluorouracil</td>
<td>400 mg/ m²</td>
<td>IV bolus</td>
<td>Over 5 minutes</td>
</tr>
<tr>
<td></td>
<td>5 Fluorouracil</td>
<td>2400 mg/ m²</td>
<td>via infusor device</td>
<td>0.9% Sodium Chloride over 46 hours</td>
</tr>
<tr>
<td>Day 3</td>
<td>Attend ward/clinic for removal of 5-FU infusor device</td>
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</table>

**DOSE FREQUENCY**

Every 14 days

**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 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 colorectal cancer
3. 1st line indication
4. Given in combination with (a) oxaliplatin based combination chemotherapy OR (b) Given in combination with irinotecan-based combination chemotherapy
5. No previous treatment with Bevacizumab

NOTE: If excessive toxicity with oxaliplatin or irinotecan, bevacizumab can be continued with a fluoropyrimidinone alone until disease progression only.

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 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.

RECOMMENDED TAKE HOME MEDICATION

Ondansetron 8mg twice daily for 2 to 3 days
Dexamethasone 4mg twice daily for 1 to 3 days
Metoclopramide 10 to 20mg 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
- 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 4th 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
FOLFOX
- Patient needs to attend on day 3 for removal of infusor
- If diarrhoea is a problem give loperamide or codeine phosphate.
- Oxaliplatin is incompatible with saline. Must use 5% dextrose as diluent and line flush
- Bronchospasm can occur. * If severe laryngeal spasm occurs consider increasing Oxaliplatin infusion to 6 hours
- *Note: A variety of calcium folinate doses have been used in clinical trials, e.g. 200mg/m² with max dose 350mg or 175mg Calcium LevoFolinate or 350mg Calcium Folinate. To enable a convenient, cost effective single vial dose, 300mg is recommended.
- As with all platinum based chemotherapy, patients may experience allergic reaction during administration. The table is intended to help differentiate between Platinum hypersensitivity and Laryngo-pharyngeal Dysesthesia.

<table>
<thead>
<tr>
<th>Clinical Symptoms</th>
<th>Laryngo-pharyngeal Dysesthesia</th>
<th>Platinum Hypersensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dyspnea</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>Bronchospasm</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Laryngospasm</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Anxiety</td>
<td>Present</td>
<td>Present</td>
</tr>
<tr>
<td>O₂ saturation</td>
<td>Normal</td>
<td>Decreased</td>
</tr>
<tr>
<td>Difficulty swallowing</td>
<td>Present (loss of sensation)</td>
<td>Absent</td>
</tr>
<tr>
<td>Pruritus</td>
<td>Absent</td>
<td>Present</td>
</tr>
<tr>
<td>Cold induced symptoms</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Blood Pressure</td>
<td>Normal or Increased</td>
<td>Normal or Decreased</td>
</tr>
<tr>
<td>Treatment</td>
<td>Anxiolytics; observation in a controlled clinical setting until symptoms abate or at physician’s discretion</td>
<td>Oxygen, steroids, epinephrine, bronchodilators; Fluids and vasopressors if appropriate</td>
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Patients who have previously experienced Grade I or II Platinum Hypersensitivity should be pre-medicated with 45 minutes prior to Oxaliplatin:
- Dexamethasone 20 mg IV in 50 mL NS over 15 minutes (or Hydrocortisone 100mg) 30 minutes prior to Oxaliplatin:
- Chlorphenamine 10 mg IV and Ranitidine 50 mg IV in 50 mL NS over 20 minutes
**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, dyspnœoa, angioedema or generalised urticaria.
- Paracetamol can be used to treat reactions.
- Bevacizumab therapy should not be initiated for at least 28 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.

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**

**FOLFOX**
- Peripheral neurotoxicity very common with Oxaliplatin. (dose limiting toxicity)
- Myelosuppression
- Cold induced parathesia
- Nausea and Vomiting
- Allergic reaction
- Diarrhoea
- Stomatitis
- Palmar/Plantar Erythrodysesthesia
- Darkening/discholoration of veins
- Cardiotoxicity - Occasionally patients may experience coronary artery spasm
- Laryngopharyngeal dysesthesia

**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:
- Delay 1 week if ANC < 1.5 and Platelets < 75 to 100
- No dose reduction for CTC grade I/II ANC
- Grade III/IV ANC → delay chemotherapy until recovered, then proceed at 20% 5FU and Oxaliplatin dose reduction
- If delay > 1 week or delay 2 weeks or greater occurs, reduce the 5FU dose (bolus & infusional) and oxaliplatin by 20%. Continue at the reduced dose for subsequent cycles unless other toxicity occurs.
- If further delay(s) for bone marrow suppression occur despite a 20% dose reduction, consider a further 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: FOLFOX
- No dose reduction should apply to oxaliplatin in case of PPE
- In case of Grade III/IV stomatitis or diarrhoea despite a 20% reduction of 5FU, Oxaliplatin should be reduced by 20%

Neurotoxicity:
- Cold related paraesthesia of hands/feet or dysesthesia/laryngeal spasm syndrome last a few hours and do not require treatment or dose reduction.
- If severe laryngeal spasm occurs consider increasing Oxaliplatin infusion to 6 hours
- If symptoms persist for 14 days and/or there is pain, functional loss, omit Oxaliplatin and continue with 5FU/FA until fully recovered, then restart Oxaliplatin at 20% dose reduction

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)
- No information on dose adjustment. The kidneys and liver are not major organs for bevacizumab metabolism or excretion.

TREATMENT LOCATION
Cancer Centre or Cancer Unit where there is an Oncologist with a specialisation in Colorectal cancer patients as appropriate.
REFERENCES

- Bevacizumab summary of product characteristics (SPC) available at https://www.medicines.org.uk/emc/medicine/15748/SPC/Avastin+25mg+ml+concentrate+for+solution+for+infusion/
- Common Terminology Criteria. for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.02: Sept. 15, 2009 Available at http://www.acrin.org/Portals/0/Administration/Regulatory/CTCAE_4.02_2009-09-15_QuickReference_5x7.pdf

<table>
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<tr>
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<tr>
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<tr>
<td>Prepared By:</td>
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