Bevacizumab 10mg/kg and Pegylated liposomal DOXOrubicin (CAELYX®) 40mg/m² Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
For the treatment of adult patients with platinum-resistant recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer who received no more than two prior chemotherapy regimens and who have not received prior therapy with bevacizumab or other VEGF inhibitors or VEGF receptor–targeted agents.	C56 C57 C48	00772a	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

Bevacizumab is administered on Days 1 and 15 and pegylated liposomal DOXOrubicin (CAELYX®) is administered on Day 1 of a 28 day cycle until disease progression or unacceptable toxicity occurs.

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1, 15	Bevacizumab	10mg/kg	IV infusion	100ml NaCl 0.9% over 90mins[a]	Every 28 days
1	Pegylated Liposomal DOXOrubicin (Caelyx®)	40mg/m²	IV infusion	[b]250ml glucose 5% at rate of 1mg/min for first cycle (see note)	Every 28 days

[a] The initial dose of bevacizumab 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.
Flush line with NaCl 0.9% pre and post bevacizumab dose as it should not be mixed with glucose solutions.

[b] For doses ≥ 90mg, use 500mL infusion bag.

Do not use with in-line filters.
NOTE: If no infusion reaction observed subsequent infusions may be administered over 60min.
For patients who experience an infusion reaction, the method of infusion should be modified as follows: 5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.

ELIGIBILITY:

- Indication as above
- ECOG status 0-2
- Adequate organ function

EXCLUSIONS:

- Hypersensitivity to bevacizumab, liposomal pegylated DOXOrubicin or to any of the excipients
- Pregnancy
- Breast feeding
- Hypersensitivity to Chinese Hamster Ovary (CHO) cell products or other recombinant human or humanised antibodies
- Pre-existing cardiac myopathy or congestive heart failure
- Hepatic dysfunction (see Dose Modifications below)

USE WITH CAUTION:

Use with caution in patients with:

- Previous pelvic radiotherapy
- Pre-existing uncontrolled hypertension
- Clinically significant cardiovascular disease
- Renal disease including proteinuria
- Bleeding/Clotting disorders
- Previous anthracycline exposure
- History of significant venous thromboembolism
- Recent (less than 6 months) arterial thromboembolic events
- Prior radiation to the chest wall or other serious medical illness

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Dipstick urinalysis for protein
- Blood pressure measurement, cardiac assessment including history and physical exam
- ECG
- MUGA / ECHO (to determine LVEF)
- INR if clinically indicated*.

Regular tests:

- FBC, renal and liver profile
- Dipstick urinalysis for protein
- Blood pressure prior to each cycle and post treatment
- INR if clinically indicated*
- ECG
- MUGA/ECHO** (to determine LVEF as clinically indicated)

*(For patients on warfarin, weekly INR until stable warfarin dose established, then INR prior to each cycle.)
**See Adverse Effects/Regimen specific complications for guidelines regarding cardiotoxicity

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant
- Bevacizumab dose reduction for adverse events is not recommended (SmPC). If indicated, bevacizumab therapy should either be permanently discontinued or temporarily suspended until toxicity resolves (Table 4 and Table 5).
- Dose reductions for pegylated liposomal DOXOrubicin (CAELYX®) are outlined below.

Haematological:

Table 1: Recommended dose modification of pegylated liposomal DOXOrubicin (CAELYX®) for haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose
1.5-1.9	and	≥75	**100%**
1-<1.5	or	50-74	Wait until ANC ≥ 1.5 and platelets ≥ 75; redose with no dose reduction
0.5-<1	or	<50	Wait until ANC ≥ 1.5 and platelets ≥ 75; redose with no dose reduction
<0.5	or	<25	Wait until ANC ≥ 1.5 and platelets ≥ 75; decrease dose by 25% or continue full dose with growth factor support.

Renal and Hepatic Impairment:

Table 2: Recommended dose modification for bevacizumab and pegylated liposomal DOXOrubicin (CAELYX®) in renal and hepatic impairment

Drug	Renal Impairment	Hepatic Impairment	
Bevacizumab	No studies have been performed in patients with renal impairment.	No studies have been performed in patients with hepatic impairment.	
Pegylated liposomal DOXOrubicin (CAELYX®)	No dose reduction necessary	**Bilirubin (micromol/L)**	**Dose**
		20-51	75%
		>51	50%

Management of adverse events:

Table 3: Dose Modification of pegylated liposomal DOXOrubicin (CAELYX®) for Palmar-Plantar Erythrodysesthesia (PPE) and Stomatitis

Week after prior pegylated liposomal DOXOrubicin dose			
Toxicity Grade At Current Assessment	**Day 1 of new cycle**	**Delayed one week**	**Delayed 2 weeks**
Grade 1	**Proceed with dose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case delay 1 week	**Proceed with dose unless** patient has experienced a previous Grade 3 or 4 skin toxicity or stomatitis, in which case delay another week	PPE and stomatitis: Decrease dose by 25%; OR Stomatitis: Consider discontinuation - clinician decision
Grade 2	Delay 1 week	Delay an additional week	PPE and stomatitis: Decrease dose by 25%; OR Stomatitis: Consider discontinuation - clinician decision
Grade 3	Delay 1 week	Delay an additional week	Discontinue
Grade 4	Delay 1 week	Delay an additional week	Discontinue

Proteinuria:

Table 4: Dose modifications of bevacizumab for proteinuria

Degree of proteinuria	Action
Neg or 1+ dipstick or less than 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled
2+ or 3+ dipstick or greater than or equal to 1 g/L laboratory urinalysis for protein	Administer bevacizumab dose as scheduled. Collect 24-hour urine for determination of total protein within 3 days before the next scheduled bevacizumab administration. Adjust bevacizumab treatment based on the table below
If urine dipstick shows 4+ at baseline or during treatment	Withhold bevacizumab and proceed with 24 hour urine collection.
24-hour urine total protein (g/24hr)	**Action**
less than or equal to 2	Proceed
greater than 2 to 4	Hold dose and recheck 24 hour urine every 2 weeks, resume therapy when less than or equal to 2g/24hour
greater than 4	Discontinue Therapy

Table 5: Dose modifications of bevacizumab for adverse events

Drug	Adverse reactions	Recommended dose modification
Bevacizumab	Hypertension: Uncontrolled or symptomatic hypertension on Day 1	Withhold bevacizumab treatment, start antihypertensive therapy or adjust pre-existing medication
	*Grade 4 hypertension or persisting grade 3 hypertension	Discontinue bevacizumab
	Grade 4 Proteinuria	Discontinue bevacizumab
	Tracheoesophageal (TE) fistula or any Grade 4 fistula	Discontinue bevacizumab
	Grade 4 Thromboembolic events	Discontinue bevacizumab
	Haemorrhagic event ≥ Grade 3	Discontinue bevacizumab
	Gastrointestinal Perforation	Discontinue bevacizumab

*National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v.3)

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Bevacizumab: Minimal **(Refer to local policy).**
Pegylated liposomal DOXOrubicin (CAELYX®): Low **(Refer to local policy).**

PREMEDICATIONS: Not usually required unless the patient has had a previous hypersensitivity.

OTHER SUPPORTIVE CARE:

Anti-diarrhoeal treatment may be required **(Refer to local policy).**

Other strategies to prevent and treat PPE, which may be initiated for 4 to 7 days after treatment with pegylated liposomal DOXOrubicin include keeping hands and feet cool, by exposing them to cool water (soaks, baths, or swimming), avoiding excessive heat/hot water and keeping them unrestricted (no socks, gloves, or shoes that are tight fitting) (**Refer to local policy**).

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS:

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

Bevacizumab

- **Gastrointestinal perforations:** Patients may be at an increased risk for the development of gastrointestinal perforation and gall bladder perforation 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.
- **Wound healing complications:** 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. In patients who experienced wound healing complications during therapy, treatment should be withheld until the wound is fully healed. Therapy should be withheld for major elective surgery for 28 days and for 7 days for minor surgery or as directed by the prescribing Consultant. Necrotising fasciitis, including fatal cases, has rarely been reported in patients treated with bevacizumab. This 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.
- **Hypertension:** An increased incidence of hypertension has been observed in patients treated with bevacizumab. Clinical safety data suggest that the incidence of hypertension is likely to be dose-dependent.
    - Pre-existing hypertension should be adequately controlled before starting bevacizumab treatment. Bevacizumab may be continued in conjunction with standard anti-hypertensive therapy at physician's discretion.
    - Patients should have their blood pressure measured before each dose or more frequently if hypertension develops/worsens.
    - Any patient who develops hypertension (>150/100 mmHg) should be treated with anti-hypertensive medications, or have their pre-existing medications adjusted. Patients developing severe hypertension (>200/110 mm Hg) that is not controlled with medication should have bevacizumab discontinued.
    - It should be permanently discontinued if the patient develops hypertensive crisis or hypertensive encephalopathy.

- **Posterior Reversible Encephalopathy Syndrome (PRES):** There have been rare reports of bevacizumab-treated patients developing signs and symptoms that are consistent with PRES, 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 PRES requires confirmation by brain imaging, preferably magnetic resonance imaging (MRI). In patients developing PRES, treatment of specific symptoms including control of hypertension is recommended along with discontinuation of bevacizumab. The safety of reinitiating therapy in patients previously experiencing PRES is not known.
- **Proteinuria:** Patients with a history of hypertension may be at increased risk for the development of proteinuria.
- **Thromboembolism:** Patients receiving bevacizumab plus chemotherapy, with a history of arterial thromboembolism or age > 65 years have an increased risk of developing arterial thromboembolic reactions during therapy. Caution should be taken when treating these patients. Therapy should be permanently discontinued in patients who develop arterial thromboembolic reactions. Patients may be at risk of developing venous thromboembolic reactions, including pulmonary embolism under bevacizumab treatment. Bevacizumab should be discontinued in patients with life-threatening (Grade 4) thromboembolic reactions, including pulmonary embolism. Patients with thromboembolic reactions ≤ Grade 3 need to be closely monitored.
- **Haemorrhage:** Patients treated with bevacizumab have an increased risk of haemorrhage, especially tumour associated haemorrhage and minor mucocutaneous haemorrhage. Bevacizumab should be used with caution in patients at risk of bleeding.
- **Aneurysms and artery dissections**: The use of VEGF pathway inhibitors in patients with or without hypertension may promote the formation of aneurysms and/or artery dissections. Before initiating bevacizumab, this risk should be carefully considered in patients with risk factors such as hypertension or history of aneurysm.

Pegylated liposomal DOXOrubicin:

- **Cardiotoxicity**: Frequent ECG monitoring is recommended. Reduction of the QRS complex suggests cardiac toxicity. LVEF monitoring using ECHO or MUGA should be applied during treatment. The evaluation of LVEF is considered to be mandatory before each additional administration of pegylated liposomal DOXOrubicin that exceeds a lifetime cumulative anthracycline dose of 450mg/m^2. Cardiac toxicity also may occur at cumulative anthracycline doses lower than 450mg/m^2 in patients with prior mediastinal irradiation or in those receiving concurrent cyclophosphamide therapy.
- **Acute Infusion Reaction:** Usually seen during the first infusion. For patients who experience an infusion reaction, the method of infusion should be modified as follows: 5% of the total dose should be infused slowly over the first 15 minutes. If tolerated without reaction, the infusion rate may then be doubled for the next 15 minutes. If tolerated, the infusion may then be completed over the next hour for a total infusion time of 90 minutes.
- **Palmar-plantar erythrodysesthesia syndrome (PPE**): Monitor patient for presence of PPE. If present, patient may require an interruption in treatment (see dose modifications).
- **Extravasation**: Pegylated liposomal DOXOrubicin is considered an irritant **(Refer to local guidelines).**

DRUG INTERACTIONS:

- The safety and efficacy of concomitant administration of radiotherapy and bevacizumab has not been established.
- No interaction studies have been performed between EGFR antibodies and bevacizumab. EGFR monoclonal antibodies should not be administered for the treatment of mCRC in combination with bevacizumab-containing chemotherapy. Results from the randomised phase III studies, PACCE and CAIRO-2, in patients with mCRC suggest that the use of anti-EGFR monoclonal antibodies panitumumab and cetuximab, respectively, in combination with bevacizumab plus chemotherapy, is associated with decreased PFS and/or OS, and with increased toxicity compared with bevacizumab plus chemotherapy alone.
- Concurrent use of bevacizumab and sunitinib can increase the risk of microangiopathic haemolytic anaemia (MAHA).
- No formal medicinal product interaction studies have been carried out for pegylated liposomal DOXOrubicin.
- Exercise caution in the concomitant use of pegylated liposomal DOXOrubicin with products known to interact with standard DOXOrubicin hydrochloride.
- Current drug interaction databases should be consulted for more information.

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1	14/11/2022		Prof. Maccon Keane

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