Gemcitabine, Carboplatin and Bevacizumab

Indication

Second line advanced epithelial ovarian, fallopian tube or primary peritoneal cancer.
WHO performance status 0 or 1.

Bevacizumab funding needs to be agreed before commencing treatment.

ICD-10 codes

Codes prefixed with C48, 56, 57.

Regimen details

Day	Drug	Dose	Route
1	Bevacizumab	15mg/kg	IV infusion
1	Carboplatin	AUC 4*	IV infusion
1 and 8	Gemcitabine	1000mg/m^2	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) an EDTA should be performed.
CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

6 cycles of chemotherapy.
Bevacizumab continued until disease progression or unacceptable toxicity.

Administration

Bevacizumab is administered as an intravenous infusion in sodium chloride 0.9% to a final concentration of between 1.4 to 16.5mg/mL. Doses up to 1650mg are administered in 100mL sodium chloride 0.9%, doses greater than 1650mg are administered in 250mL sodium chloride 0.9%.

Bevacizumab may be administered before or after chemotherapy.

The first infusion must be given over 90 minutes. If tolerated, the next infusion can be given over 60 minutes; if this is also tolerated, subsequent infusions can be given over 30 minutes.

Bevacizumab should not be initiated for at least 35 days following major surgery or until the wound is fully healed. For elective surgery, bevacizumab should be withheld for 35 days. For minor surgery (including port placement) bevacizumab should be withheld for 7 days following surgery.

Carboplatin is administered in 250-500mL glucose 5% over 30-60 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.

If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of carboplatin and appropriate therapy.

Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Pre-medication

Chlorphenamine 10mg IV and hydrocortisone 100mg IV may be given if there has been more than a 6 month gap between courses of treatment due to a possible reaction to carboplatin antibodies.

Emetogenicity

Day 1 has a moderate - high emetogenic potential
Day 8 has moderate – low emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Loperamide if required.
H_2 antagonist or proton pump inhibitor if required.
Consider ciprofloxacin 250-500mg BD days 5-14 (10 days total) following febrile neutropenia.
Antihypertensives may be required to manage hypertension commonly observed with bevacizumab therapy.

Extravasation

Bevacizumab and Gemcitabine are neutral (Group 1)
Carboplatin is an irritant (Group 3)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
CA125	28 days
Blood pressure (BP)	on day 1
Proteinuria (dipstick)	on day 1

Baseline EDTA if suspected or significant renal dysfunction.
Cardiac assessment is also required with ECHO for patients with significant cardiac history or prior chest wall radiation or anthracycline treatment.
Pre-existing hypertension should be adequately controlled before commencing treatment.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Blood pressure	Before each dose (more frequently if hypertension)
Proteinuria (dipstick)	Before each dose*

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant.

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 30mL/min (and <10% change in CrCl from previous cycle)

Dose modifications

Dose reduction is not recommended for bevacizumab; doses should be withheld or discontinued.

- **Haematological toxicity**

Day	**Neutrophils** (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose modification**	
				Carboplatin	**Gemcitabine**
Day 1	≥ 1.0	and	≥ 100	100%	100%
	0.5 – 1.0	or	50-99	Delay then75%	Delay then 75%
	< 0.5	or	< 50	Delay then 75%	Delay then 75%
Day 8	≥ 1.0	and	≥ 100	N/A	100%
	0.5 – 1.0	or	50-99	N/A	75%
	<0.5	or	< 50	N/A	Omit

In the case of febrile neutropenia reduce dose of carboplatin and gemcitabine to 80% and consider prophylactic ciprofloxacin for future cycles (see supportive medication).

- **Renal impairment**

If calculated CrCl falls by >10% from previous cycle, consider dose recalculation. If calculated CrCl improves the dose should not be increased unless there is a clear cause of renal function improvement (such as treatment of urinary tract obstruction).

CrCl (mL/min)	**Carboplatin dose**	**Gemcitabine dose**
> 30	100%	100%
20-30	EDTA then 100% dose	Consider dose reduction (consultant decision)
< 20	Omit	Consider dose reduction (consultant decision)

There is no data regarding administration of bevacizumab in patients with renal impairment and dose modification should not be required. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Carboplatin dose**	**Gemcitabine dose**
≤ 1.5	and	≤ 1.5	100%	100%
1.5-3	or	1.5-3.5	100%	80%
> 3	or	> 3.5	Not recommended (consultant decision)*	

*transient increases in liver enzymes have been seen in patients being treated with both carboplatin and gemcitabine although no dose reduction is usually required.

There is no data regarding administration of bevacizumab in patients with hepatic impairment and dose modification should not be required. Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant.

- **Other toxicities**

Carboplatin and Gemcitabine

For all other grade 3-4 toxicities (except alopecia) delay treatment until resolved to ≤ grade 1 and resume with 80% dose of carboplatin and gemcitabine. If further toxicity occurs consider additional dose reduction (discuss with consultant).

If delays of > 3 weeks or > 2 dose reductions, discontinue treatment.

Bevacizumab

Toxicity	Definition	Dose adjustment
Infusion related reactions	Grade ≤ 2	**90 minute infusion**: premedication prior to next dose and give over 90 minutes (if tolerated may reduce infusion duration for future cycles with premedication) **60 minute infusion**: all subsequent doses should be given over 90 minutes with premedication. **30 minute infusion**: all subsequent doses should be given over 60 minutes with premedication.
	Grade >2	Discontinue bevacizumab
Hypertension	Grade 1 Increase of >20 mmHg (diastolic) or >140/90 mmHg (previously within normal limits) asymptomatic and transient (<24 hours)	Recheck 1 hour later: - if <140/90 mmHg – administer as normal - if 140/90 mmHg - 150/100 mmHg –administer and recheck BP 48 hours later (commence antihypertensives if BP remains >140/90 mmHg). - if >150/100 mmHg – omit and recheck BP 48 hours later(commence antihypertensives if BP remains >140/90 mmHg).
	Grade 2 Recurrent or persistent (> 24 hours) increase by 20 mmHg (diastolic) or to > 140/90 mmHg if previously within normal limits	Withhold bevacizumab. Commence antihypertensive medication. Once BP <140/90 mmHg restart treatment.
	Grade 3 Persistent BP > 140/90mmHg, requiring increase in antihypertensive treatment	Withhold bevacizumab. If hypertension cannot be controlled permanently discontinue treatment.
	Grade 4 Hypertensive crisis	Permanently discontinue bevacizumab.
Proteinuria	1+ or 2+	Continue bevacizumab.
	3+	Continue bevacizumab, with 24 hour urinalysis prior to next cycle, then: - if <2g continue treatment with 24 hour urinalysis prior to each dose. If falls to <1g return to dipstick analysis. - if ≥2g withhold until repeat urinalysis <2g then restart treatment with 24 hour urinalysis prior to each dose.
	4+	Withhold bevacizumab. 24 hour urinalysis. Then treat as above.
	Nephrotic syndrome	Permanently discontinue bevacizumab

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Pulmonary fibrosis (rare)
Nephrotoxicity
Arterial/venous thromboembolism
GI perforation, fistulas
Osteonecrosis of the jaw
Reversible posterior leukoencephalopathy
Wound healing complications
Haemolytic uraemic syndrome*

Gemcitabine should be discontinued at the first sign of microangiopathic haemolytic anaemia (such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevated bilbirubin, creatinine, blood urea nitrogen or LDH). Renal failure may not be reversible with discontinuation of therapy, dialysis may be required.

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Constipation, diarrhoea
Stomatitis and mucositis
Fatigue
Rash
Oedema
Ototoxicity
Electrolyte disturbances
Hypertension
Proteinuria

- **Other side effects**

Mild alopecia
Elevated transaminases

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

<u>Carboplatin only</u>:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Bevacizumab is contraindicated in patients who have a history of hypersensitivity reaction to bevacizumab or other recombinant human or humanized antibodies.

Bevacizumab should be used with caution in patients with:
• Untreated central nervous system metastases

- Uncontrolled hypertension
- History or risk factors for thromboembolic events
- Significant cardiac risk factors for development of congestive heart failure

References

- Summary of Product Characteristics - Bevacizumab (Roche) accessed 17 Sept 2014 via www.medicines.org.uk
- NHS England Cancer Drug Fund List. Accessed 17 Sept 2014 via www.england.nhs.uk
- Summary of Product Characteristics Carboplatin (Hospira) accessed 17 Sept 2014 via www.medicines.org.uk
- Summary of Product Characteristics Gemcitabine (Lilly) accessed 17 Sept 2014 via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4th ed. Radcliffe Medical Press. 2002.

Written/reviewed by: Dr R Bowen (Consultant Oncologist, Royal United Hospital, Bath), Dr A Walther (Consultant Oncologist, UHBristol NHS Trust)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

Date: 11 December 2014