Carboplatin, Paclitaxel and Bevacizumab (gynae)

Indication

First line treatment of recurrent or metastatic stage IVB cervical cancer. WHO performance status 0 or 1.

First line treatment of stage III or IV epithelial ovarian, fallopian tube or primary peritoneal cancer. Bevacizumab to start with 1st or 2nd cycle of chemotherapy following surgery or with 1st or 2nd cycle of chemotherapy in patients with stage IV or inoperable disease.

ICD-10 codes

Codes pre-fixed with C48, 53, 56, 57.

Regimen details

First line treatment of recurrent or metastatic cervical cancer:

Day	Drug	Dose	Route
1	Bevacizumab	15mg/kg	IV infusion
1	Paclitaxel	175mg/m²	IV infusion
1	Carboplatin	AUC 5 or 6*	IV infusion

To continue until disease progression or unacceptable toxicity.

First line treatment of advanced epithelial ovarian, fallopian tube or primary peritoneal cancer:

Day	Drug	Dose	Route
1	Bevacizumab	7.5mg/kg Or 15mg/kg*	IV infusion
1	Paclitaxel	175mg/m²	IV infusion
1	Carboplatin	AUC 5 or 6*	IV infusion

*15mg/kg induction dose may be used if planning dual maintenance therapy with bevacizumab and olaparib

Chemotherapy to continue for 6 cycles.
Single agent Bevacizumab maintenance at 7.5mg/kg to continue until disease progression or unacceptable toxicity for a maximum of 15 months.

* 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) a formal GFR measurement should be performed. . If using measured GFR, consider dosing at AUC 5. If using Cockcroft and Gault, consider dosing at AUC 6.
CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

As above

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 28 days following major surgery or until the wound is fully healed. For elective surgery, bevacizumab should be withheld for 28 days following surgery. For minor surgery (including port placement) bevacizumab should be withheld for 7 days following surgery.

Paclitaxel is administered in a 500mL sodium chloride 0.9% non-PVC infusion bag with a 0.22 micron in-line filter over 3 hours.
Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion.

Carboplatin should be 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 bevacizumab, paclitaxel or 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 bevacizumab, paclitaxel or carboplatin and appropriate therapy should be initiated.

Pre-medication

30 minutes prior to each paclitaxel infusion:
Chlorphenamine 10mg IV slow bolus
Dexamethasone 16-20mg IV slow bolus

Emetogenicity

Carboplatin/Paclitaxel/Bevacizumab has moderate- high emetic potential.
Bevacizumab monotherapy has low emetic potential

Additional supportive medication

Proton pump inhibitor if required.
Loperamide if required.
Laxatives if required
Mouthwashes as per local policy.
Antihypertensives may be required to manage hypertension commonly observed with bevacizumab therapy.

Extravasation

Bevacizumab is neutral (Group 1)
Carboplatin – irritant (Group 3)
Paclitaxel – vesicant (Group 5)

Investigations – pre first cycle

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

Perform baseline measured GFR 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 cycles 2-6

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

* If 3+ on dipstick perform 24 hour urinalysis and delay bevacizumab until <2g/24 hours.

Investigations – pre bevacizumab maintenance cycles

Investigation	**Validity period** (or as per local policy)
FBC	3 monthly
U+E (including creatinine)	3 monthly
LFTs	3 monthly
Calcium	3 monthly
Magnesium	3 monthly
Blood pressure	Before each dose (more frequently if hypertension)
Proteinuria (dipstick)	Before each dose*

* If 3+ on dipstick perform 24 hour urinalysis and delay bevacizumab until <2g/24 hours.

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
Bilirubin	< 1 x ULN
AST/ALT	< 5 x ULN
Creatinine Clearance (CrCl)	> 30 mL/min (and < 10% change)

Dose modifications

Paclitaxel

Dose level	Paclitaxel dose
Full dose	175mg/m^2
First dose reduction	135mg/m^2
Second dose reduction	90mg/m^2
Third dose reduction	Discontinue

Carboplatin – reduce by dose by 1 x AUC

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

- **Haematological toxicity**

Neutrophils (x 10^9/L)		**Platelets** (x 10^9/L)	**Carboplatin dose**	**Paclitaxel dose**
≥ 1.0	and	≥ 100	100%	100%
< 1.0	or	< 100	Delay 1 week (or until recovery) then reduce dose by 1 x AUC	Delay 1 week (or until recovery)
< 1.0	and	< 100	Delay 1 week (or until recovery) then reduce dose by 1 x AUC	Delay 1 week (or until recovery) then reduce dose to next dose reduction level

In the case of febrile neutropenia (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 135mg/m^2 an carboplatin by 1 x AUC dose for all future cycles.

- **Renal impairment**

If calculated CrCl falls by >10% from previous dose, consider dose recalculation.

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	Measured GFR then 100% dose (or consider changing to non-nephrotoxic regimen, discuss with consultant)
< 20	Discuss with consultant

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)	**Paclitaxel dose**
≤1.25	and	<10	100%
1.25-2	and		135mg/m^2
2-5	and		90mg/m^2
> 5	or	≥10	Not recommended (consultant decision)

Carboplatin – no need for dose adjustment expected. Consultant decision if bilirubin > 5 x ULN or ALT ≥ 10 x ULN.

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 Paclitaxel

Toxicity	Definition	Carboplatin dose	Paclitaxel dose
Fatigue	Grade 3	100%	1st occurrence – 135mg/m^2, if persistent 90mg/m^2 or omit
Neuropathy	Grade 2	100%	1st occurrence – 135mg/m^2 for all future cycles, if persistent 90mg/m^2 or omit
	Grade ≥ 3		Withhold until ≤ Grade 1, restart at 90mg/m^2.
Arthralgia/Myalgia	Grade ≥ 2	100%	Consider diclofenac +/- cocodamol or prednisolone 10mg BD for 5 days starting 24 hours post paclitaxel. If persists reduce dose to 135mg/m^2

For all other grade 3 toxicities (except alopecia and nausea and vomiting) withhold until grade ≤ 1 and continue with carboplatin with 1 x AUC dose reduction and paclitaxel 135mg/m^2. If further toxicity, consider additional dose reduction, discuss with consultant.

For any grade 4 toxicity (except alopecia and nausea and vomiting) withhold and discuss with consultant.

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 ≥160/100mmHg	Withhold bevacizumab. If persistent, escalate antihypertensive treatment If hypertension cannot be controlled permanently discontinue treatment.
	Grade 4 Hypertensive crisis	Permanently discontinue bevacizumab.

Bevacizumab continued

Toxicity	Definition	Dose adjustment
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

- **Rare or serious side effects**

Myelosuppression
Hypersensitivity reactions
Pulmonary fibrosis, pneumonitis
Nephrotoxicity
Electrolyte disturbances
Arrhythmias
Cardiac failure
Arterial/venous thromboembolism
GI perforation, fistulas
Osteonecrosis of the jaw
Reversible posterior leukoencephalopathy
Wound healing complications

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue
Hypertension
Proteinuria

- **Other side effects**

Flu-like symptoms
Taste changes
Headache
Abdominal pain
Deranged liver function
Rash
Ototoxicity

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

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Clozapine: increased risk of agranulocytosis, avoid concomitant use.

Paclitaxel is a CYP 2C8 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Carboplatin only:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
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 Carboplatin (Hospira) accessed 12 Aug 2021 via www.medicines.org.uk
- Summary of Product Characteristics Paclitaxel (Accord) accessed 12 Aug 2021 via www.medicines.org.uk
- Summary of Product Characteristics - Avastin (Roche) accessed 12 Aug 2021 via www.medicines.org.uk
- Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment – supplementary appendix. *Lancet Oncol* 2019; **20:** e201–08.
- Perren T J, Swart A M, Pfisterer J, Ledermann JA et al. A Phase 3 Trial of Bevacizumab in Ovarian Cancer. N Engl J Med 2011; 365:2484-2496.

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Date: August 2021