Carboplatin, Paclitaxel, Bevacizumab and Pembrolizumab (Gynae)

Indication

Treatment of persistent, recurrent or metastatic cervical cancer, in adults whose tumours express PD-L1 with a combined positivity score (CPS) of at least 1. WHO performance status 0 or 1.

(NICE TA939)

ICD-10 codes

Codes prefixed with C56

Regimen details

NB. Treatment may be given with or without Bevacizumab.

Cycles 1-6

Day	Drug	Dose	Route
1	Pembrolizumab	200mg	IV infusion
1	Bevacizumab	15mg/kg	IV infusion
1	Paclitaxel	175mg/m^2	IV infusion
1	Carboplatin	AUC 5*	IV infusion

*Carboplatin dose calculated using the Calvert equation: Carboplatin dose (mg) = AUC (CrCl +25). Creatinine clearance should be capped at 125mL/min for dosing. 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.

Cycles 7 onwards

Day	Drug	Dose	Route
1	Bevacizumab	15mg/kg 3 weekly	IV infusion
1	Pembrolizumab	200mg 3 weekly Or 400mg 6 weekly	IV infusion

Cycle frequency

21 Days

Number of cycles

Up to 6 cycles in combination with platinum chemotherapy
Maintenance pembrolizumab (with or without bevacizumab) may continue for a total of 2 years (or a maximum of 35 3-weekly cycles) or until disease progression or unacceptable toxicity, whichever occurs first.

Administration

Pembrolizumab should be administered in 100mL sodium chloride 0.9% over 30 minutes.

Pembrolizumab should be administered via an infusion set with an in-line sterile, non-pyrogenic, low protein binding filter (pore size 0.2 – 5.0µm).

After the infusion the line should be flushed with 30mL sodium chloride 0.9%.

Patients should be monitored every 30 minutes during the infusion (blood pressure, pulse and temperature) and for infusion related reactions. For mild to moderate reactions, decrease the infusion rate and closely monitor. Premedication with paracetamol and chlorphenamine should be used for further doses. For severe infusion related reactions discontinue treatment.

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.

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 pembrolizumab 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/Pembrolizumab has a moderate/high emetic potential – refer to local policy
Bevacizumab/Pembrolizumab has a 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.
Anti-emetics as per local policy if required

Extravasation

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

Investigations – pre first cycle

Investigation	Validity period (or as per local policy)
FBC	14 days
U&Es (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days
Thyroid function	14 days
Glucose	14 days
Cortisol	At consultant discretion
Blood pressure	on day 1 (if bevacizumab to be administered)
Proteinuria (dipstick)	on day 1 (if bevacizumab to be administered)

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 subsequent cycles

Investigation	Validity period (or as per local policy)
FBC	96 hours (7 days if Pembrolizumab/Bevacizumab only)
U&Es (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	7 days
Thyroid function	6 weekly
Glucose	As clinically indicated
Cortisol	As clinically indicated
Blood pressure	Before each dose of bevacizumab (more frequently if hypertension)
Proteinuria (dipstick)	Before each dose of bevacizumab*

If 3+ of dipstick, perform 24 hour urinalysis and delay Bevacizumab until <2g/24 hours. Consider renal complication of immunotherapy.

Standard limits for administration to go ahead

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

Investigation	Limit
Neutrophil count	≥ 1.0 $X10^9$/L
Platelets	≥ 100 $X10^9$/L
Creatinine Clearance (CrCl)	≥ 30ml/min (and <10% change during carboplatin treatment)
Bilirubin	< 1 x ULN
ALT/AST	< 3 x ULN
Alkaline Phosphatase	< 5 x ULN

Dose modifications

Paclitaxel

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

Carboplatin-reduce dose by 1 x AUC

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

- **Haematological toxicity**

Neutrophils (x10^9/L)		Platelets (x10^9/L)	Carboplatin dose	Paclitaxel dose
≥1.0	**and**	≥100	100%	
<1.0	**or**	<100	Delay 1 week (or until recovery) then reduce dose by 1 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 and carboplatin by 1 x AUC dose for all future cycles.

No dose adjustments are required for bevacizumab or pembrolizumab.

- **Renal impairment**

Carboplatin- 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

Paclitaxel- no dose modifications required

Bevacizumab- There is no data regarding administration of bevacizumab in patients with renal impairment and dose modification should not be required.

Pembrolizumab- The safety and efficacy of pembrolizumab has not been studied in patients with renal impairment. No specific dose adjustments are recommended in mild to moderate renal impairment. Discuss with consultant if CrCl <30mL/min. See below for management of nephritis during pembrolizumab treatment.

Deteriorating organ function may be a sign of disease progression and so should be discussed with consultant

- **Hepatic impairment**

Paclitaxel

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.

Bevacizumab- There is no data regarding administration of bevacizumab in patients with hepatic impairment and dose modification should not be required.

Pembrolizumab- The safety and efficacy of pembrolizumab has not been studied in patients with hepatic impairment. No specific dose adjustments are recommended in mild hepatic impairment. See below for management of hepatitis.

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 NSAID +/- 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.
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

Pembrolizumab

Immune reactions may occur during or after completion of treatment. Management may require treatment delay and corticosteroids (initial dose of 1-2 mg/kg/day prednisolone or equivalent followed by a taper).

Toxicity	**Definition**	**Action/Dose adjustment**
Colitis	Grade 1	Continue and closely monitor
	Grade 2-3	Withhold until symptoms resolve to ≤ grade 1
	Grade 4	Permanently discontinue pembrolizumab
Pneumonitis	Grade 1	Continue and closely monitor
	Grade 2	Withhold until symptoms resolve to ≤ grade 1
	Grade 3-4 or recurrent grade 2	Permanently discontinue pembrolizumab
Nephritis	Grade 2 (creatinine 1.5-3x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine >3 x ULN)	Permanently discontinue pembrolizumab

Toxicity	Definition	Action/Dose adjustment
Endocrine	Symptomatic hypophysitis	Withhold until symptoms resolve to ≤ grade 1
	Type 1 diabetes with >grade 3 hyperglycaemia (glucose >13.9 mmol/L or ketoacidosis	Withhold until ≤ grade 2 May recommencing after corticosteroid taper or discontinue
	Hyperthyroidism ≥ grade 3	Withhold until ≤ grade 2 May consider recommencing after corticosteroid taper or discontinue
	Hypothyroidism	Continue and manage with replacement therapy
Hepatitis	AST/ALT 3-5 x ULN or Bilirubin > 1.5-3 x ULN	Withhold until symptoms resolve to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue pembrolizumab
	If liver metastasis with baseline AST/ALT 3-5 x ULN: - If AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab
Skin Reactions	Grade 3 or suspected Stevens-Johnson syndrome (SJS) or toxic epidermal necrolysis (TEN)	Withhold until resolves to ≤ grade 1
	Grade 4 or confirmed SJS or TEN	Permanently discontinue
Other immune-related adverse events	Grade 3 or 4 myocarditis Grade 3 or 4 encephalitis Grade 3 or 4 Guillain-Barre Syndrome	Permanently discontinue

Pembrolizumab should be permanently discontinued if:
- Grade 4 toxicity (except for endocrinopathies that are controlled with replacement hormones)
- Corticosteroid dosing cannot be reduced to ≤10 mg prednisolone or equivalent per day within 12 weeks
- Treatment-related toxicity does not resolve to Grade 0-1 within 12 weeks after last dose
- Any event occurs a second time at Grade ≥ 3 severity

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

- **Serious side effects**

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

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Myelosuppression
Diarrhoea, constipation
Peripheral neuropathy
Oedema
Phlebitis
Myalgia, arthralgia
Alopecia
Fatigue
Hypertension
Proteinuria
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Rash, pruritus
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Flu-like symptoms
Taste changes
Abdominal pain
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

Corticosteroids: use of systemic corticosteroids at baseline, before starting pembrolizumab, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of pembrolizumab. However, systemic corticosteroids or other immunosuppressants can be used after starting pembrolizumab to treat immune-related adverse reactions.

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

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.

References

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