Pembrolizumab, carboplatin, paclitaxel (+/- bevacizumab) for persistent, recurrent or metastatic cervical cancer

Indication

Persistent, recurrent or metastatic cervical cancer with CPS score ≥1

Regimen details

Cycles 1-6:

Pembrolizumab	200mg intravenous **or** 395mg subcutaneous
Paclitaxel	175mg/m^2 intravenous
Carboplatin	AUC 5 intravenous

(substitute cisplatin 50-60mg/m^2 for carboplatin in case of carboplatin contraindication)

Bevacizumab 15mg/kg should be added where safe to do so (see separate regimen)

Cycles 7+

Pembrolizumab	400mg intravenous **or** 790mg subcutaneous

Cycle frequency

Cycles 1-6 given every 3 weeks
Cycles 7+ given every 6 weeks

(Cycles 7+ can be given every 3 weeks if patient has toxicity)

Number of cycles

Until disease progression or unacceptable toxicity. Pembrolizumab is limited to 2 years treatment (35 cycles of 3-weekly treatment or the equivalent when given 6-weekly)

Administration

Pembrolizumab subcutaneous

Inject into the subcutaneous tissue of the thigh or abdomen, avoiding the 5 cm area around the navel. Do not inject into skin that is damaged, sore, bruised, scarred, scaly, or has red patches. Rotate injection sites for subsequent injections.

- Inject 395mg over 1 minute
- Inject 790mg over 2 minutes

Pembrolizumab intravenous

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%

Paclitaxel

Paclitaxel is administered in a 250-500mL 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

Paclitaxel must be administered before carboplatin

Carboplatin

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 paclitaxel or carboplatin. Facilities for the treatment of hypotension and bronchospasm and anaphylaxis must be available.

If hypersensitivity reactions occur, consult "Protocol for the management of hypersensitivity to carboplatin and taxane-based chemotherapy" document

Pre-medication

Chlorphenamine 10mg IV
Dexamethasone 20mg IV
Ondansetron 8mg IV
H_2 antagonist – 1 hour before treatment.

Emetogenicity

Moderate

Additional supportive medication

Extravasation

Carboplatin – irritant
Paclitaxel -vesicant
Pembrolizumab - neutral

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Thyroid function tests	14 days
Glucose, HBA1c	14 days
Calcium, Phosphate	14 days
Cortisol	14 days
CK	14 days
Amylase	14 days
Troponin	14 days
Hepatitis B, Hepatitis C and HIV screen	14 days
Follicle stimulating hormone	14 days
Luteinizing hormone	14 days
Testosterone	14 days

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST), Bone, Magnesium.
TFT, random glucose, random cortisol, CK, amylase and troponin (every 6 weeks)

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	≥ 1.5 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 30 mL/min and no more than 10% change to baseline
Bilirubin	See below

AST	See below

Dose modifications

Haematological toxicity

Neutrophils (x 10^9 /L)		Platelets (x 10^9 /L)	Carboplatin dose	Paclitaxel dose
≥ 1.5	And	≥ 100	100%	100%
< 1.5	And / or	50 - 100	Delay 1 week or until recovery. If longer than 1 week, then reduce dose by 1 AUC level. If isolated neutropenia, GCSF can be used, +/-/or dose reduction.	Delay 1 week or until recovery. If longer than 1 week, then reduce dose to 135-150mg/m^2. If isolated neutropenia, GCSF can be used, +/-/or dose reduction.
Any		<25 or <50 with bleeding	Delay 1 week or until recovery. Then reduce dose by at least 20%	Delay 1 week or until recovery. Then reduce dose by 20% (bear in mind: thrombocytopenia is driven more by carboplatin)
Febrile neutropenia			Delay 1 week or until recovery. Then reduce dose by at least 20%	Delay 1 week or until recovery. Then reduce dose by at least 20%

If a second episode of neutropenic fever or thrombocytopenia requiring dose reduction occurs, another minimum 25% dose reduction of carboplatin and paclitaxel is recommended. Chemotherapy should be discontinued if a third episode occurs.
If a dose reduction is required due to low neutrophils or platelets, then that dose reduction is maintained for subsequent cycles.

Renal Impairment

Adjust dose of carboplatin if serum creatinine increases by >10% of baseline

Hepatic Impairment

Bilirubin (x ULN)		AST/ALT (x ULN)	Carboplatin dose	Paclitaxel dose
<1.25	And	<5	100%	100%
1.25 – 2	And		100%	Delay to recovery and reduce to 50-75% dose
2 – 5	And		80-100%	omit
>5	Or	≥5	(Not recommended – consultant decision)	

Neuropathy

Grade 2: Reduce paclitaxel dose to 135mg/m^2 at first occurrence, if further deterioration omit
Grade 3 or above: withhold until grade ≤ 1 then restart at 100mg/m^2. Omit if persistent / recurrence

Immunotherapy Toxicity

Consider immunotherapy driven toxicity as a potential reason for all changing laboratory results and discuss with a consultant if any concerns

Immunotherapy toxicities should be aggressively managed as can cause permanent and life-threatening complications.
Refer to UKONS and ESMO guidance for treatment of immune related toxicities.
Available at:
https://www.healthierlsc.co.uk/canceralliance/chemotherapy-protocols/immunotherapy-toxicity-guidelines

Toxicity	Definition	Action
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 1 (creatinine ≤ 1.5 x ULN)	Continue and closely monitor
	Grade 2 (creatinine 1.5-3 x ULN)	Withhold until symptoms resolve to ≤ grade 1
	Grade 3 (creatinine > 3 x ULN)	Permanently discontinue pembrolizumab
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 consider 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 resolves to ≤ grade 1
	AST/ALT > 5 x ULN or Bilirubin > 3 x ULN	Permanently discontinue pembrolizumab
	Liver metastasis and baseline AST/ALT 3-5 x ULN but AST/ALT increases ≥ 50% for ≥ 1 week	Permanently discontinue pembrolizumab
Infusion-related reactions	Grade 3-4	Permanently discontinue pembrolizumab

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 prednisone 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
- Grade 3 or 4 myocarditis
- Grade 3 or 4 encephalitis
- Grade 3 or 4 Guillain-Barré syndrome
- Grade 3 or 4 or recurrent pneumonitis

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Pneumonitis
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Myelosuppression
Reduced appetite
Headache
Dizziness
Dry eyes
Cough
Constipation
Nausea
Diarrhoea
Hypertension (particularly if also receiving bevacizumab)
Low magnesium
Neuropathy
Allergic reactions
Rash
Fatigue
Myalgias
Hyperglycaemia
Hypocalcaemia

- **Other side effects**

Arthralgia
Alopecia

Significant drug interactions

– for full details consult product literature/ reference texts

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.

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

Paclitaxel is a CYP 2C8/9 and CYP 3A4 substrate. Drug levels may be increased by inhibitors of these enzymes and decreased by inducers of these enzymes.

Carboplatin

Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Women of childbearing potential should use effective contraception during treatment and for at least 4 months after the last dose.

References

Colombo et al. Pembrolizumab for Persistent, Recurrent, or Metastatic Cervical Cancer N Engl J Med 2021;385:1856-67

THIS PROTOCOL HAS BEEN DIRECTED BY DR HOGG, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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