Pembrolizumab and paclitaxel for advanced breast cancer

Indication

First line treatment of locally advanced unresectable or metastatic triple negative breast cancer in patients with PD-L1 expression test results of immune cell (IC) <1% and a combined positive score (CPS) of 10 or more

Regimen details

Pembrolizumab can be given intravenously or subcutaneously at a frequency of every 3 or 6 weeks

Dose	Route	Frequency
200mg	IV infusion	Every 3 weeks
400mg	IV infusion	Every 6 weeks
395mg	Subcutaneous	Every 3 weeks
790mg	Subcutaneous	Every 6 weeks

Paclitaxel 90mg/m^2 intravenous infusion on days 1, 8 and 15 of a 28-day cycle

Note: due to the difference in cycle lengths with pembrolizumab and paclitaxel, this must be prescribed as two separate regimens on iQemo

Cycle frequency

As above

Number of cycles

Given until disease progression or unacceptable toxicity.
Pembrolizumab must be stopped after 2 years

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

Intravenous pembrolizumab

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 1 hour.

Blood pressure and pulse should be monitored regularly (e.g. every 30 minutes) during paclitaxel infusion. 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. 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 paclitaxel and appropriate therapy should be initiated.

Pre-medication

30 minutes before paclitaxel

Chlorphenamine 10mg	I.V. bolus
Ranitidine 50mg (or other H_2 antagonist)	50mls 0.9% sodium chloride
Dexamethasone 10mg	100mls 0.9% sodium chloride

For subsequent weeks reduce dexamethasone dose to 8mg then 4mg then stop dexamethasone.

If patient experiences any hypersensitivity reaction do not reduce the dexamethasone dose further but continue the same or increased dose of dexamethasone
Stop H_2 antagonist after 3 doses if paclitaxel tolerated

Emetogenicity

Minimal

Additional supportive medication

None

Extravasation

Pembrolizumab – neutral
Paclitaxel - vesicant

Investigations – pre first cycle

Investigation	**Validity period**
FBC	14 days
U+E (including creatinine)	14 days
LFT inc AST	14 days
Thyroid function	14 days
Glucose	14 days
Calcium	14 days
Cortisol	Baseline
Luteinising hormone	Baseline
Follicle stimulating hormone	Baseline
Testosterone	Baseline

Investigations –pre subsequent cycles

FBC, U+E (including creatinine), LFT (including AST) before each dose of paclitaxel
Magnesium once a month, random glucose or BM once a month
TFTs every 6 weeks
Consultation every three 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	≥ 1.0 x 10^9/L
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 30 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN
Alkaline phosphatase	< 5 x ULN

Dose modifications

Haematological toxicity

Pembrolizumab:
Discuss with the consultant if:
Neutrophils < 1.0 x 10^9/L
Platelets <75 x 10^9/L

Paclitaxel:
If neutrophils < 1.0 x 10^9/L and/or platelets < 100 x 10^9/L delay for 1 week then resume at 100% dose. If delayed for > 1 week discuss with consultant.
In the case of febrile neutropenia reduce paclitaxel to 60mg/m^2 for all future doses.

Renal impairment:

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

Paclitaxel:
No dose adjustment necessary

Hepatic impairment

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.

Paclitaxel: Paclitaxel is not recommended in severe hepatic impairment. If bilirubin < 1.5 x ULN and AST/ALT < 5 x ULN proceed with 100% dose. For more severe hepatic impairment, treatment may only proceed on consultant's decision, at a reduced dose with weekly monitoring of LFTs

Infusion reactions

Consult network guidelines for managing hypersensitivity reactions and rechallenge

Immunotherapy related toxicities

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

Adverse effects –

for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Teratogenicity
Hypersensitivity reactions
Pneumonitis
Hepatic impairment
Cardiotoxicity
Electrolyte disturbances
Arrhythmias
Colitis
Hepatitis
Nephritis
Endocrinopathies
Pancreatitis

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea, constipation
Peripheral neuropathy
Neuropathy
Myalgia, arthralgia
Alopecia
Fatigue
Anorexia
Rash
Hyperglycaemia
Hypocalcaemia
Hyperthyroidism, hypothyroidism

- **Other side effects**

Insomnia, depression, anxiety
Headache, dizziness
Skin reactions
Nail changes
Eye problems

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

Pembrolizumab: 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 immunerelated adverse reactions.

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.

Additional comments

References

Cortes, J. et al. Pembrolizumab plus chemotherapy versus placebo plus chemotherapy for previously untreated locally recurrent inoperable or metastatic triple-negative breast cancer (KEYNOTE-355): a randomised, placebo-controlled, double-blind, phase 3 clinical trial. Lancet 2020; 396:1817-1828

THIS PROTOCOL HAS BEEN DIRECTED BY DR MARTIN HOGG, DESIGNATED LEAD CLINICIAN FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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