Pembrolizumab carboplatin paclitaxel EC/AC for early breast cancer

Indication

Triple negative breast cancer (neoadjuvant), stage cT1c N1-2 or cT2-4d N0-2

Regimen details

Drug	Dosage	Route	Frequency
Pembrolizumab	200mg	IV	3-weekly
Paclitaxel	80mg/m^2	IV	Weekly
Carboplatin	AUC5 (Max dose 790mg)	IV	3-weekly
For 4 cycles, followed by:			
Pembrolizumab	200mg	IV	3-weekly
Doxorubicin*	60mg/m^2	IV	3-weekly
Cyclophosphamide	600mg/m^2	IV	3-weekly
For 4 cycles, followed by:			
Pembrolizumab	400mg	IV	6-weekly
For a further 5 cycles			

*or epirubicin 90mg/m^2

Cycle frequency

As above

Number of cycles

As above

Administration

Pembrolizumab is to be given before chemotherapy, via a 0.2µm in-line filter in 100ml 0.9% sodium chloride over 30 minutes

Paclitaxel is to be given after pembrolizumab and before carboplatin. See below for pre-medication

Paclitaxel is given via a 0.2µm in-line filter in 250ml 0.9% sodium chloride over 1 hour

Carboplatin is given in 500ml 5% glucose over 1 hour

Patients must be monitored for infusion reactions

Epirubicin/doxorubicin and cyclophosphamide are given into the side port of a fast flowing drip

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.

Continue to give dexamethasone 8mg as anti-emetic pre-med for carboplatin day 1.

If patient experiences any hypersensitivity reaction do not reduce the dexamethasone dose further but continue the same or increased dose of dexamethasone. If severe reaction, change regimen/remove offending agent

Stop H_2 antagonist after 3 doses if paclitaxel tolerated

Emetogenicity

Carboplatin/paclitaxel day 1: moderate
Carboplatin/paclitaxel day 8 & 15: minimal
Doxorubicin (or epirubicin) & cyclophosphamide: high
Pembrolizumab alone: minimal

Additional supportive medication

Pegfilgrastim 6mg subcutaneous 24 hours after chemotherapy on cycles 5-8

Extravasation

Pembrolizumab – neutral
Paclitaxel – vesicant
Carboplatin – irritant
Doxorubicin/epirubicin – vesicant
Cyclophosphamide - neutral

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
MUGA/echocardiogram	Before doxorubicin/epirubicin

Investigations –pre subsequent cycles

FBC U&Es and LFTs – before each dose of chemotherapy
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 (day 1)	$\geq 1.0 \times 10^9$/L
Neutrophil count (day 8 & 15)	$\geq 0.8 \times 10^9$/L
Platelet count (day 1)	$\geq 100 \times 10^9$/L
Platelet count (day 8 & 15)	$\geq 75 \times 10^9$/L
Creatinine clearance	≥ 60 mL/min
Bilirubin	≤ 1.5 x ULN
AST	< 1.5 x ULN

Dose modifications

Haematological toxicity:

Cycles 1-4

In the event of haematological toxicity, delay day 1 treatment for 7 days. Paclitaxel should be omitted on day 8 or 15, not delayed

If treatment is delayed for 2 weeks, or if platelets fall below 25, reduce carboplatin dose by 25%

Cycles 5-6

In the event of haematological toxicity, delay day 1 treatment for 7 days

If treatment is delayed for 2 weeks, or if febrile neutropenia occurs, reduce dose of doxorubicin (or epirubicin) and cyclophosphamide by 25%

Non-haematological toxicity:

<table>
<tr><td>Renal</td><td>Carboplatin: review serum creatinine result at each cycle, recalculate carboplatin dose if creatinine has increased by >20%</td></tr>
<tr><td>Hepatic</td><td>
<table>
<tr><td></td><td>Epirubicin/Doxorubicin</td><td>Cyclophosphamide</td></tr>
<tr><td>Bilirubin µmol/L</td><td>Dose</td><td>Dose</td></tr>
<tr><td>24 to 50</td><td>50%</td><td>100%</td></tr>
<tr><td>51 to 85</td><td>25%</td><td>75%</td></tr>
<tr><td>Above 85</td><td>Omit</td><td>Omit</td></tr>
</table>
Paclitaxel
<table>
<tr><td>Bilirubin less than 1.25 times ULN and AST < 10 x ULN</td><td>Give 100% dose</td></tr>
<tr><td>Bilirubin greater than 1.25 times ULN</td><td>Consider dose reduction</td></tr>
<tr><td>Alk Phos more than 3 times ULN</td><td>Consider dose reduction</td></tr>
</table>
</td></tr>
<tr><td>Peripheral Neuropathy</td><td>NCI-CTC grade 2 peripheral neuropathy withhold paclitaxel only until the neuropathy recovers to grade 1 then dose reduce by 10mg/m2 If NCI-CTC grade 3 peripheral neuropathy occurs, discontinue paclitaxel and proceed to EC part of regimen</td></tr>
<tr><td>Myalgia/Arthralgia</td><td>Often co-exist, usually grade 1 or 2. Manage with reassurance that the condition is self-limiting. NSAIDs may be considered but they may be ineffective</td></tr>
<tr><td>Infusion reactions</td><td>Carboplatin & paclitaxel:
Consult network guidelines for managing hypersensitivity reactions and rechallenge

Pembrolizumab:
Discontinue pembrolizumab in the event of a grade 3 or 4 infusion reaction</td></tr>
<tr><td>Mucositis</td><td>Reduce epirubicin/doxorubicin by 20% in the event of grade 3 or 4 mucositis</td></tr>
</table>

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

Nausea
Alopecia
Anemia
Neutropenia
Fatigue
Diarrhoea
Elevated liver enzymes
Vomiting
Asthenia
Constipation
Rash
Peripheral neuropathy
Infusion reactions
Hypothyroidism
Hyperthyroidism
Skin reaction
Adrenal insufficiency

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.

Phenytoin: requires close monitoring if using concurrently.

Cyclophosphamide
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Azathioprine: increased risk of hepatotoxicity
Clozapine: increased risk of agranulocytosis – avoid concomitant use
CYP2B6 and CYP3A4 inhibitors (Nevirapin, Ritonavir): co-administration may reduce the efficacy of cyclophosphamide
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Grapefruit juice: decreased or delayed activation of cyclophosphamide. Patients should be advised to avoid grapefruit juice for 48 hours before and on day of cyclophosphamide dose

Carboplatin
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
Yellow fever vaccine: contraindicated

Paclitaxel:
Clozapine: increased risk of agranulocytosis.
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

Schmid et al. Pembrolizumab for Early Triple-Negative Breast Cancer N Engl J Med 2020; 382:810-821

THIS PROTOCOL HAS BEEN DIRECTED BY DR HOGG, LEAD ONCOLOGIST FOR BREAST CANCER

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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