Pertuzumab/Trastuzumab (subcutaneous) and paclitaxel heredERA trial

Indication

For use in heredERA trial only

Metastatic breast or locally recurrent unresectable breast cancer in patients whose tumours are HER2 positive (IHC 3+ or ISH positive) and who have not received previous anti-HER2 therapy or chemotherapy for their metastatic disease

Regimen details

Pertuzumab/trastuzumab 1200mg/600mg subcutaneous injection with cycle 1 (subsequent doses 600mg/600mg)
Paclitaxel 80mg/m^2 intravenous on days 1, 8 & 15

Cycle frequency

Every 3 weeks

Number of cycles

Given for a maximum of 8 cycles then proceed to enrolment for maintenance phase

Administration

The first dose of pertuzumab/trastuzumab should be given subcutaneously over 8 minutes and the patient observed for a period of 30 minutes before any subsequent administration of chemotherapy
If tolerated, subsequent doses of pertuzumab/trastuzumab should be given subcutaneously over 5 minutes and the patient observed for 15 minutes before any subsequent administration of chemotherapy

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

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 docetaxel and therefore 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. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of paclitaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with paclitaxel

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

Low

Additional supportive medication

None routinely prescribed

Extravasation

Paclitaxel is a vesicant

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
Bone profile	14 days
MUGA scan/echocardiogram to assess LVF	Baseline

Cautions

Cardiac dysfunction (see below)
Uncontrolled hypertension or angina
Known allergies to animal proteins
Raised levels of liver enzymes (see below)

Investigations –pre subsequent cycles

1. FBC/U&Es/LFT - weekly
2. The liver function test may be retrospectively looked at (i.e. after the chemotherapy treatment) unless they are known to be abnormal then they need to be repeated the day before so that the results are available pre-chemotherapy
3. LVEF assessment by MUGA or ECHO every 6 months

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 (contact consultant if 1.2-1.5)
Platelet count	≥ 100 x 10^9/L
Creatinine clearance	≥ 20 mL/min
Bilirubin	≤ 1.5x ULN
AST	≤ 5x ULN

Dose modifications

Haematological toxicity:

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 (neutrophils < 0.5 × 10^9/L and fever > 38.5°C requiring IV antibiotics) reduce paclitaxel to 60mg/m2 for all future doses.

Renal impairment

No dose modifications required

Hepatic impairment

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.

Neuropathy

Grade	Paclitaxel dose
2	Reduce to a maximum of 70mg/m2 for all subsequent doses
≥3	Discontinue

For any other grade ≥ 2 toxicities (except alopecia) withhold until grade ≤ 1 and continue with 70mg/m^2 dose. If delayed for > 1 week, discuss with consultant

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

Left ventricular dysfunction
Pertuzumab and trastuzumab should be withheld for at least 3 weeks for any of the following:
- Signs and symptoms suggestive of congestive heart failure (Pertuzumab should be discontinued if symptomatic heart failure is confirmed)
- A drop in left ventricular ejection fraction (LVEF) to less than 40%
- A LVEF of 40%-45% associated with a fall of ≥ 10% points below pre-treatment values.

Pertuzumab and trastuzumab may be resumed if the LVEF has recovered to > 45% or 40-45% associated with <10% points below pre-treatment value.
If after a repeat assessment within approximately 3 weeks, the LVEF has not improved, or has declined further, discontinuation of Pertuzumab and trastuzumab should be strongly considered, unless the benefits for the individual patient are deemed to outweigh the risks

Dose Delays
If the interval between subsequent doses of pertuzumab/trastuzumab is greater than 6 weeks then a loading dose of 1200mg/600mg should be administered

Adverse effects –

for full details consult product literature/ reference texts

Hypersensitivity, myelosuppression, neuropathy, sepsis, pneumonitis, cardiotoxicity, nausea, vomiting, diarrhoea, injection site reactions

Significant drug interactions

– for full details consult product literature/ reference texts

CYP3A4 Enzyme inducers/inhibitors: in vitro studies suggest that CYP3A inhibitors (such as ketoconazole, ritonavir, clarithromycin and erythromycin) may raise paclitaxel levels, whereas CYP3A inducers (such as rifampicin and barbiturates) may reduce docetaxel levels

References

Phesgo SPC - https://www.medicines.org.uk/emc/product/11988
Paclitaxel SPC - https://www.medicines.org.uk/emc/product/3891/smpc

THIS PROTOCOL HAS BEEN DIRECTED BY DR HOGG, CONSULTANT ONCOLOGIST AND PRINCIPAL INVESTIGATOR FOR THE hereERA TRIAL

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

Date: October 2022
Review: October 2024
VERSION: 1