EC DOCETAXEL PERTUZUMAB / TRASTUZUMAB (Phesgo) SC (neoadjuvant node positive)

INDICATION (ICD10) C50

Check the most recent Blueteq eligibility criteria before prescribing. Blueteq registration required. (www.england.nhs.uk/publication/national-cancer-drugs-fund-list/) (PER2a)

1. Neoadjuvant pertuzumab in HER2 3+ NODE POSITIVE patients for previously untreated neoadjuvant treatment of locally advanced, inflammatory or early breast cancer at high risk of recurrence (stage T2-T4b and M0 disease) in combination with taxane chemotherapy. (TA424)

REGIMEN

Cycles 4 to 7 drugs can be given on any day ie 1 or 2. When given in combination with a taxane on the same day the pertuzumab and trastuzumab should be administered 30 minutes before the taxane.

Cycles 1 to 3

Day 1 EPIRUBICIN 100mg/m^2 IV bolus
CYCLOPHOSPHAMIDE 500mg/m^2 IV bolus

Cycle 4

Day 1 *PERTUZUMAB with TRASTUZUMAB 1800mg SC over 8 minutes
Premedication: Dexamethasone 8mg BD starting 24 hours before chemotherapy (or 20mg IV on day of chemotherapy) and 8mg bd post-chemotherapy for 2 days
DOCETAXEL 75mg/m^2 in 250ml sodium chloride 0.9% IV infusion over 60 minutes

Cycles 5 to 7

Day 1 *PERTUZUMAB with TRASTUZUMAB 1200mg SC over 5 minutes
Premedication: Dexamethasone 8mg BD starting 24 hours before chemotherapy (or 20mg IV on day of chemotherapy) and 8mg bd post-chemotherapy for 2 days
DOCETAXEL 75mg/m^2 in 250ml sodium chloride 0.9% IV infusion over 60 minutes

*For patients unable to receive SC pertuzumab / trastuzumab (phesgo) see the pertuzumab trastuzumab IV substitution regimen for IV pertuzumab plus IV trastuzumab doses, observation times etc.

Pertuzumab / Trastuzumab loading dose - observation time post injection 30 minutes
Pertuzumab / Trastuzumab maintenance doses - observation time post injection 15 minutes

CYCLE FREQUENCY AND NUMBER OF CYCLES

Every 21 days for 7 cycles
Then prescribe or ertuzumab / Trastuzumab (Phesgo) SC (adjuvant) regimen for 14 cycles to complete 18 cycles Anti her2 therapy
It is acknowledged that in patients who are node positive and whose blood counts have not recovered post neoadjuvant chemotherapy and there is a consequent delay to surgery, such patients may receive additional cycles of pertuzumab plus trastuzumab pre-surgery in order to ensure there is no break in anti-HER2 therapy.
It is also acknowledged that such patients may continue with pertuzumab plus trastuzumab after surgery pending determination of status as to pathological complete remission or not.

ANTI-EMETICS

High risk day 1 cycles 1 to 3 (consider aprepitant)
Low risk day 1 cycles 4 to 7

CONCURRENT MEDICATION REQUIRED

Docetaxel	Ensure premedication given before docetaxel. This can reduce the incidence and severity of fluid retention as well as the severity of hypersensitivity reactions. Loperamide prn every docetaxel cycle
Pertuzumab with Trastuzumab	Infusion related chills and/or fevers – treat with paracetamol and chlorphenamine.
GCSF	GCSF for 7 days starting at least 24 hours after chemotherapy

EXTRAVASATION AND TYPE OF LINE / FILTERS

Cyclophosphamide – neutral
Docetaxel – exfoliant
Epirubicin – vesicant

Filters not required
Central (or peripheral) line

INVESTIGATIONS

Blood results required before SACT administration
FBC, U&E and LFTs every cycle cycles 1 to 7
Neutrophils x 10^9/L ≥1.0 (0.8-1.0 on the day of chemo go ahead with GCSF support as per local policy).
Platelets x 10^9/L ≥100
Baseline weight and every cycle for cycles 1 to 7, then 3 monthly weight.
Monitor cardiac function according to network guidelines. Baseline LVEF greater than or equal to 55% or if anthracyclines were given that the LVEF was greater than or equal to 50% after completion of the anthracycline component of the neo-adjuvant chemotherapy.

MAIN TOXICITES AND ADVERSE REACTIONS

Cyclophosphamide	may irritate bladder, drink copious volumes of water.
Epirubicin	Cardiotoxicity – monitor cardiac function. Epirubicin may be stopped in future cycles if signs of cardiotoxicity e.g. cardiac arrhythmias, pericardial effusion, tachycardia with fatigue.
Docetaxel	Cutaneous reactions, peripheral neuropathy or fluid retention, hypersensitivity reactions
Pertuzumab with Trastuzumab	Cardiotoxicity - monitor cardiac function. Injection related chills, fevers or headache, slow the rate of injection or pause and appropriate medical therapies administered (Treatment including oxygen, beta agonists, antihistamines, rapid intravenous fluids and antipyretics may also help alleviate systemic symptoms.). For severe injection related reactions discontinue permanently. Other symptoms may include nausea, hypertension, vomiting, pain, rigors, headache, cough, dizziness, rash, and asthenia. Febrile neutropenia, diarrhea, pulmonary events Cardiomyopathy: Pertuzumab with trastuzumab administration can result in subclinical and clinical cardiac failure manifesting as CHF, and decreased LVEF, with greatest risk when administered concurrently with anthracyclines. Evaluate cardiac function prior to and during treatment. Discontinue pertuzumab with trastuzumab for cardiomyopathy.

INTERACTIONS WHICH MAY REQUIRE DOSE MODIFICATIONS
(not exhaustive list check SPC/BNF/Stockleys)

Cyclophosphamide	Cytochrome P450 enzyme inducers (e.g. rifampicin, carbamazepine, phenytoin, St Johns Wort, corticosteroids): may increase active cyclophosphamide metabolites. Allopurinol, Cimetidine and protease inhibitors: may increase active metabolites. Aprepitant, Ciprofloxacin, Fluconazole, Itraconazole: may reduce activation of cyclophosphamide and alter the effectiveness of treatment. 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.

DOSE MODIFICATIONS
Pertuzumab with trastuzumab
Delay more than 6 weeks since last dose
The loading dose of pertuzumab with trastuzumab 1800mg SC (equivalent to pertuzumab 1200mg and trastuzumab 600mg (1200/600mg vial)) should be readministered for 1 dose
then followed by maintenance doses of pertuzumab with trastuzumab 1200mg SC (equivalent to pertuzumab 600mg and trastuzumab 600mg (600/600mg vial)).

Epirubicin maximum lifetime dose
= 650mg/m^2 (in patients with cardiac dysfunction or exposed to mediastinal irradiation)
= 1000mg/m^2 (with normal cardiac function)

Haematological
Previous neutropenic sepsis, Symptoms including diarrhoea, mucositis and leucopenia, discuss with Registrar or Consultant

Docetaxel
In patients who experienced either febrile neutropenia, neutrophil count <0.5x10^9/L for more than one week, severe or cumulative cutaneous reactions or severe peripheral neuropathy during docetaxel therapy, the dose of docetaxel should be reduced from 75 to 60mg/m². If the patient continues to experience these reactions at 60mg/m², the treatment should be discontinued.

Non-haematological
Docetaxel
Discuss dose reductions if severe cutaneous reactions, peripheral neuropathy or fluid retention after previous course.

Pertuzumab with Trastuzumab
Continuation and discontinuation of pertuzumab and trastuzumab based on interval LVEF assessment as per network guidelines

Hepatic impairment
Docetaxel

ALT and/or AST >1.5xULN and ALP >2.5xULN	recommended SPC dose for 100mg/m^2 is give 75mg/m^2
Bilirubin >ULN and ALT and AST >3.5xULN with ALP >6xULN	should not be used unless strictly indicated.

Epirubicin

Bilirubin 24-51micromol/L	give 50% dose
Bilirubin 52-85micromol/L or AST >4xULN	give 25% dose
Bilirubin >86micromol/L or Child Pugh C	not recommended

Renal impairment

Cyclophosphamide

CrCl 10-29ml/min	Consider giving 75% dose

REFERENCES

1. Effects of Chemotherapy and hormonal therapy for early breast cancer on recurrence and 15 year survival: an overview of the randomised trials. EBCTG. Lancet 2005; 365: 1687–1717
2. APHINITY Trial NEJM 2017: 377:122-131