Docetaxel, Carboplatin, Trastuzumab and Pertuzumab (subcutaneous)

Indication
Neoadjuvant treatment of locally advanced, inflammatory or early breast cancer at high risk of recurrence in patients with HER2 positive disease

Regimen details
Pertuzumab/trastuzumab 1200mg/600mg subcutaneous injection with cycle 1 (subsequent doses 600mg/600mg)
Docetaxel 75mg/m^2 in 250ml 0.9% sodium chloride over 60 minutes
Carboplatin AUC6 in 500ml 5% glucose over 60 minutes

Cycle frequency
Repeat every 3 weeks

Number of cycles
6 cycles, followed by further 12 cycles of trastuzumab or trastuzumab/pertuzumab combination or 14 cycles of trastuzumab emtansine (Kadcyla)

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

Docetaxel is given intravenously over 60 minutes

Carboplatin is given intravenously over 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 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 docetaxel and appropriate therapy. Patients who have developed severe hypersensitivity reactions should not be re-challenged with docetaxel

Pre-medication
Paracetamol 1g 30-60 minutes before treatment, and regularly for 24 hours after treatment
Dexamethasone orally 8mg twice daily, start 24 hours before docetaxel

Emetogenicity
Moderate

Additional supportive medication
Patients should receive GCSF support with either pegfilgrastim 6 mg SC 24-48h post treatment or filgrastim 5 mcg/kg SC on days 3-9) with each cycle

Investigations – pre first cycle

Investigation	Validity period
FBC	14 days
U+E (including creatinine)	14 days
LFT (including AST)	14 days
MUGA or echocardiogram	Baseline

Cautions

- Uncontrolled hypertension or angina
- Cardiac dysfunction (requires monitoring as below)
- Raised levels of liver enzymes (see below)
- Hypersensitivity reactions
- Elderly patients

Investigations –pre subsequent cycles

FBC/U&Es/LFTs/Bone every 3 weeks during chemotherapy, then every 3 months when on trastuzumab single agent
LVEF assessment on MUGA or ECHO once during neoadjuvant treatment and every 12 weeks during adjuvant treatment
Investigations and consultations prior to each cycle:
FBC U&Es and LFTs
Magnesium once a month, random glucose or BM once a month
Consultation every three weeks
The U&Es and LFTs need to be checked the day before so that results are available pre-chemotherapy

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 (calculated)	≥ 30 mL/min
Bilirubin	≤ ULN
AST	≤ 1.5 x ULN
Alkaline phosphatase	≤ 2.5 x ULN

Dose modifications

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay 1 week or until recovery.
Following an episode of febrile neutropenia reduce docetaxel to 60mg/m^2 and carboplatin dose by 1 x AUC for all future doses

If thrombocytopenia (nadir platelets ≤ 50 x 10^9 /L) reduce docetaxel to 60mg/m^2 and carboplatin dose by 1 x AUC for all future doses

Hepatic impairment

AST/ALT (x ULN)		Alkaline phosphatase (x ULN)	Docetaxel dose
≤ 1.5	And	< 2.5	100%
>1.5	Or	≥ 2.5- 6	75%
> 3.5	Or	≥ 6	Discuss with consultant

If bilirubin > 1.0 x ULN – contact consultant

Other toxicity

Toxicity	Definition	Docetaxel dose
Peripheral neuropathy	Grade 2	75%
	Grade 3 or 4	Discuss with consultant
Diarrhoea*	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%
Stomatitis	Grade 3 or 4	1st occurrence – 75%
		2nd occurrence – 60%

*Consider interrupting pertuzumab treatment in the event of severe diarrhoea

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

Serious side effects

Secondary malignancy
Myelosuppression
Infusion related reactions
Anaphylaxis
Interstitial pneumonitis
Teratogenicity
Infertility
Cardiotoxicity

Common side effects

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Peripheral neuropathy
Arthralgia and myalgia

Other side effects

Alopecia
Fluid retention
Deranged liver function

Phlebitis
Skin toxicity
Nail changes

Additional comments

Carboplatin dose is calculated using calculated creatinine clearance
Dose = (CrCl + 25) x AUC

Significant Drug Interactions

Warfarin/coumarin anticoagulants: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

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

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

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THIS PROTOCOL HAS BEEN DIRECTED BY DR BEZECNY, CONSULTANT ONCOLOGIST

RESPONSIBILITY FOR THIS PROTOCOL LIES WITH THE HEAD OF SERVICE

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