Docetaxel, Carboplatin, Trastuzumab (Herceptin ®) and Pertuzumab

Indication

Neoadjuvant treatment of high risk, HER 2 positive breast cancer where anthracyclines are unsuitable or contra-indicated.

(NICE TA424)

ICD-10 codes

Codes with a prefix C50

Regimen details

Cycle 1 – loading:

Day	Drug	Dose	Route
1	Pertuzumab	840mg	IV infusion
1	Trastuzumab	8mg/kg	IV infusion
1	Docetaxel	75mg/m^2	IV infusion
1	Carboplatin	AUC 6*	IV infusion

Due to the potential for hypersensitivity reactions, for the first cycle pertuzumab may be administered on day 1 and trastuzumab, docetaxel and carboplatin on day 2 or as per local practice.

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) an EDTA should be performed. If using an EDTA consider dosing at AUC 5 and if using Cockcroft and Gault consider dosing at AUC 6.
CrCl should be capped at 125mL/min.

Cycles 2-6:

Day	Drug	Dose	Route
1	Pertuzumab	420mg	IV infusion
1	Trastuzumab	6mg/kg	IV infusion
1	Docetaxel	75mg/m^2	IV infusion
1	Carboplatin	AUC 6*	IV infusion

If the dosing interval is > 4 weeks for trastuzumab or ≥ 6 weeks for pertuzumab, a further loading dose will be required.

Following surgery adjuvant trastuzumab (Herceptin®) should be continued to complete 1 year of treatment. This may be given as a flat 600mg subcutaneous dose or continued as an intravenous infusion.

Cycles 7-18

Day	Drug	Dose	Route
1	Trastuzumab (Herceptin ®)	600mg or 6mg/kg	SC IV infusion

Cycle frequency
21 days

Number of cycles
6 cycles of chemotherapy.

Pertuzumab should not be administered for more than 6 cycles as neo-adjuvant treatment for early breast cancer.

Adjuvant trastuzumab (Herceptin®) should be continued to complete 1 year of treatment (maximum 18 cycles in total)

Administration
Pertuzumab and trastuzumab may be administered in either order but prior to the docetaxel and carboplatin.

Pertuzumab is administered in 250mL sodium chloride 0.9% over 60 minutes (cycle 1) followed by a 60 minute observation period (before next drug administration). For cycle 2 onwards (providing pertuzumab is well tolerated) pertuzumab may be administered over 30 minutes followed by a 30-60 minute observation period.

Trastuzumab is administered in 250mL sodium chloride 0.9% over 90 minutes (cycle 1). The patient should be observed for 6 hours (or as per local policy for trastuzumab administration) after the start of the infusion for symptoms of infusion related reactions (e.g. fever, chills). For cycle 2 onwards, (providing trastuzumab well tolerated) trastuzumab may be given over 30 minutes. Patients should be observed for 2 hours after the start of the infusion for symptoms of infusion related reactions.

It may not be necessary to stop treatment for minor hypersensitivity reactions e.g. flushing, localised rash but infusions must be stopped for major reactions, e.g. hypotension, dyspnoea, angioedema or generalised urticaria.

Docetaxel is administered as an IV infusion in 250mL or 500mL (concentration dependent) PVC free sodium chloride 0.9% over 60 minutes.

Carboplatin is administered in 250-500mL glucose 5% over 30-60 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 re-started 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.

Following surgery: cycles 7-18:
Trastuzumab may be administered by IV infusion as above or subcutaneously as a flat dose of 600mg in a volume of 5mL by subcutaneous injection over 2-5 minutes. The injection site should be alternated between left and right thigh, with new injections at least 2.5cm from the old site. Avoid administration into sites that are bruised, inflamed, tender or hard. Other medicinal products for subcutaneous administration should preferably be injected at different sites. Patients should be observed for administration related reactions for 6 hours after the first dose and 2 hours after subsequent doses (or as per local policy for trastuzumab administration).

Pre-medication

Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to chemotherapy. (Note: Patients must receive 3 doses of dexamethasone prior to treatment).
In the case where 3 doses have not been taken, dexamethasone 16-20mg IV should be administered 30-60 minutes prior to chemotherapy and the remaining 3 oral doses should be taken as normal.

Emetogenicity

This regimen has moderate-high emetic potential

Additional supportive medication

Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required.

Extravasation

Docetaxel is an exfoliant (Group 4)
Carboplatin is an irritant (Group 3)
Pertuzumab and Trastuzumab are neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Echocardiogram	Baseline

Baseline EDTA if suspected or significant renal dysfunction.

Investigations - pre subsequent cycles

Investigation	**Validity period** (or as per local policy)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Echocardiogram	Pre cycle 4 and cycle 6. Then every 3 months or according to local practice.

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥ 1.0 x 10^9/L
Platelets	≥ 100 x 10^9/L
Creatinine Clearance (CrCl)	> 30mL/min (and <10% change in CrCl from previous cycle)
Bilirubin	≤ 1.0 x ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN
Echocardiogram – LVEF	≥ Lower Limit of Normal for the institution (LLN)

Dose modifications

- **Haematological toxicity**

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.

Trastuzumab and pertuzumab may continue during periods of chemotherapy induced myelosuppression.

- **Renal impairment**

There is no data available on the use of docetaxel in severe renal impairment. No modifications required. Consultant decision if CrCl<10mL/min.

CrCl (mL/min)	**Carboplatin dose**
> 30	100%
20-30	EDTA then 100% dose
< 20	Omit

If CrCl falls by more than 10% from the previous cycle then consider a dose reduction.

No dose modification for renal function is required for trastuzumab.

Pertuzumab has not been studied in renal impairment; no dose recommendations can be made.

- **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 withhold dose (or consultant decision to treat)

Transient increases in liver enzymes have been seen in patients being treated with carboplatin although no dose reduction is usually required. If bilirubin ≥ 3 x ULN and/or transaminases ≥ 5 x ULN discuss with consultant.

No dose modification is required for trastuzumab.

Pertuzumab has not been studied in renal impairment; no dose recommendations can be made.

- **Other toxicities**

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%

*Pertuzumab may cause severe diarrhoea. If severe diarrhoea an anti-diarrhoeal treatment should be instituted and interruption of the treatment with pertuzumab should be considered if no improvement of the condition is achieved. When the diarrhoea is under control the treatment with pertuzumab may be reinstated.

Any other grade 3 or 4 toxicity- discuss with consultant.

Left ventricular dysfunction

LVEF must be above LLN for treatment to go ahead. The summary of product characteristics (SPC) for pertuzumab states that cardiac monitoring is required every 2 cycles in the neoadjuvant setting. After completion of neo-adjuvant treatment cardiac monitoring should be every 3 – 4 months whilst on trastuzumab with additional monitoring after completion according to local practice or SPC.

LVEF	Trastuzumab/Pertuzumab
> LLN	Continue
40%-LLN and decrease < 10% from baseline **and** asymptomatic	Continue. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks
40%-LNN and decrease ≥ 10% from baseline **and** asymptomatic	Withhold. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg). Repeat LVEF within 3 weeks and if not within 10% from baseline withhold treatment. Discuss with consultant and refer to cardiology
< 40%	Withhold. If BP and renal function adequate start an ACE inhibitor (eg ramipril 2.5mg) and consider a beta blocker (eg bisoprolol 2.5mg Repeat LVEF within 3 weeks and if still < 40% withhold treatment and discuss with consultant. Refer to cardiology.
Symptomatic congestive heart failure	Discontinue

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

- **Frequently occurring 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

Significant drug interactions – for full details consult product literature/ reference texts

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

There is no data regarding drug interactions with trastuzumab or pertuzumab.

Additional comments

Women of childbearing potential should use effective contraception while receiving pertuzumab and for 6 months following treatment.

References

- National Institute for Health and Clinical Excellence. TA424 accessed 12 April 2017 via www.nice.org.uk
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