Docetaxel, Trastuzumab and Pertuzumab

Indication
First line treatment of locally advanced or metastatic HER2 positive unresectable breast cancer.

(NICE TA509)

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

Due to the potential for hypersensitivity reactions, for the first cycle pertuzumab may be administered on day 1 and trastuzumab and docetaxel on day 2.

Subsequent cycles:

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

*Docetaxel may be escalated to 100mg/m^2 for subsequent cycles if the initial dose is tolerated – discuss with consultant.

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

Cycle frequency
21 days

Number of cycles
Docetaxel: usual maximum 6 cycles. Further cycles – consultant decision.
Trastuzumab and pertuzumab: until disease progression (outside the CNS) or unacceptable toxicity. Pertuzumab should not be given as monotherapy, if trastuzumab is discontinued, pertuzumab should also be discontinued.

Administration
Pertuzumab and trastuzumab may be administered in either order but the docetaxel should be administered last.

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 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.

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 unless following a risk assessed desensitisation protocol.

Pre-medication

Dexamethasone 8 mg BD (morning and lunchtime) for 3 days starting 24 hours prior to docetaxel. (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 mild - moderate emetic potential

Additional supportive medication

Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required – recommend prescribe as prophylactic treatment prior to cycle 1 to use if needed for management of diarrhoea

Extravasation

Pertuzumab and trastuzumab are neutral (Group 1)
Docetaxel is an exfoliant (Group 4)

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

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	After 3 cycles and then every 3 to 6 months or as per local policy (see below)

The above investigations are not usually required prior to every cycle once docetaxel cycles are completed, as per local policy.

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
Bilirubin	≤ 1.0 x ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN (≤ 10 x ULN if bone only metastases)
ECHOCARDIOGRAM – left ventricular ejection fraction (LVEF)	≥ Lower Limit of Normal for the institution (LNN)

Dose modifications

- **Haematological toxicity**

If neutrophils <1.0 x 10^9/L and/or platelets <100 x 10^9/L delay docetaxel 1 week or until recovery.

If febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week reduce docetaxel dose to 75% for all subsequent cycles.

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.

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 – 3.5	Or	≥ 2.5- 6	75%
> 3.5	Or	≥ 6	60% or discontinue - discuss with consultant

If AST/ALT is 1.5-2.5 x ULN and alkaline phosphatase is < 2.5 x ULN the maximum recommended dose of docetaxel is 75 mg/m^2

*unless due to bone metastases only.

If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

No dose modification is required for trastuzumab.

Pertuzumab has not been studied in severe hepatic 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 3 cycles in the metastatic setting. Local practice varies and once established on treatment cardiac monitoring is generally reduced to 3 – 6 monthly (discuss with consultant) 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**

Myelosuppression
Infusion related reactions
Anaphylaxis
Interstitial pneumonitis
Teratogenicity
Infertility
Cardiotoxicity

- **Frequently occurring side effects**

Myelosuppression
Diarrhoea
Constipation
Fatigue
Nausea and vomiting
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

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.

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

Additional comments

Women of childbearing potential should use effective contraception during and for at least 6 months following treatment.

References

- National Institute for Health and Clinical Excellence. TA509 accessed 12 June 2019 via www.nice.org.uk
- Summary of Product Characteristics Docetaxel (Sanofi Aventis) accessed on 12 June 2019 via www.medicines.org.uk
- Summary of Product Characteristics Trastuzumab (Roche) accessed on 12 June 2019 via www.medicines.org.uk
- Summary of Product Characteristics Pertuzumab (Roche) accessed on 12 June 2019 via www.medicines.org.uk
- Baselga, J., et al. Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer (2011) New Engl J Med 366(2): 109-119.

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