Docetaxel and Carboplatin (Breast)

Indication

In combination with trastuzumab (Herceptin®) for HER2 positive breast cancer.

(NICE CG80)

Early and locally advanced triple negative lymph node positive breast cancer. This may be considered after anthracyclines or where anthracyclines are contra-indicated.

ICD-10 codes

Codes with a prefix C50

Regimen details

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

* 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.

Cycle frequency

21 days

Number of cycles

4 - 6 cycles

Administration

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.

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)

Investigations – pre first cycle

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

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

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	≤ 1.5 ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase*	≤ 2.5 x ULN

*unless due to bone metastases only

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.

- **Renal impairment**

There is no data available on the use of docetaxel in severe renal impairment. No modifications required.

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.

- **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- ≥ 5	75%
> 3.5	or	≥ 5	60% or discontinue (discuss with consultant)

*unless due to bone metastases only.

If bilirubin > 1.5 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.

- **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%

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

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

Additional comments

References

- Slamon D, et al. on behalf of BCIRG006 Investigators. Phase III Randomized Trial Comparing Doxorubicin and Cyclophosphamide Followed by Docetaxel (AC T) with Doxorubicin and Cyclophosphamide Followed by Docetaxel and Trastuzumab (AC TH) with Docetaxel, Carboplatin and Trastuzumab (TCH) in Her2neu Positive Early Breast Cancer Patients: BCIRG 006 Study. San Antonio Breast Cancer Symposium, 2009; Abstract 62.
- National Institute for Health and Clinical Excellence. Clinical Guideline 81 – Advanced breast Cancer accessed 6 November 2014 via www.nice.org.uk
- Summary of Product Characteristics Docetaxel (Sanofi Aventis) accessed on 6 November 2014 via www.medicines.org.uk

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Date: 14 January 2015