Docetaxel and Cyclophosphamide (breast)

Indication

Adjuvant treatment for node positive or high risk node negative early breast cancer when an anthracycline is contra-indicated.

(NICE CG80)

ICD-10 codes

Codes with a prefix C50

Regimen details

Day	Drug	Dose	Route
1	Docetaxel	75mg/m^2	IV infusion
1	Cyclophosphamide	600mg/m^2	IV slow bolus

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.

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.

Cyclophosphamide is administered by slow IV bolus into the arm of a fast running drip of sodium chloride 0.9%. Cyclophosphamide may also be given as an IV infusion in 250-500mL sodium chloride 0.9% over 30 minutes.

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 mild - moderate emetic potential

Additional supportive medication

Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered.
GCSF is not usually required as primary prophylaxis but may be considered after occurrence of febrile neutropenia.

Extravasation

Docetaxel is an exfoliant (Group 4)
Cyclophosphamide is 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

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)	> 20 mL/min
Bilirubin	≤ 1.0 ULN
AST/ALT	≤ 1.5 x ULN
Alkaline Phosphatase	≤ 2.5 x ULN

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.

If febrile neutropenia or neutrophils < 0.5 x 10^9/L for more than 1 week consider GCSF prophylaxis for all subsequent cycles. If a second occurrence reduce doses of docetaxel and cyclophosphamide to 80% for future cycles.

- **Renal impairment**

CrCl (mL/min)	**Cyclophosphamide dose**
> 20	100%
10-20	75%
<10	50%

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

- **Hepatic impairment**

AST/ALT (x ULN)		**Alkaline phosphatase*** (x ULN)	**Docetaxel dose**	**Cyclophosphamide dose**
≤ 1.5	and	< 2.5	100%	100%
> 1.5	or	≥ 2.5- 6	75%	100%
> 3.5	or	≥ 6	Discuss with consultant	Consider dose reduction (discuss with consultant)

*unless due to bone metastases only.
If bilirubin > 1.0 x ULN withhold dose (or consultant decision to treat)

- **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
Teratogenicity
Infertility
Cardiotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Diarrhoea
Constipation
Fatigue
Nausea and vomiting
Myelosuppression
Stomatitis and mucositis
Arthralgia and myalgia
Alopecia

- **Other side effects**

Fluid retention
Deranged liver function
Phlebitis
Skin toxicity
Nail changes
Taste disturbances
Bladder irritation

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.

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Cyclophosphamide:
Amiodarone: increased risk of pulmonary fibrosis – avoid if possible
Clozapine: increased risk of agranulocytosis – avoid concomitant use
Digoxin tablets: reduced absorption – give as liquid form
Indapamide: prolonged leucopenia is possible - avoid
Itraconazole: may increase adverse effects of cyclophosphamide
Phenytoin: reduced absorption - may need to increase dose of phenytoin
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.

Additional comments

Nil

References

- Summary of Product Characteristics Taxotere® (Docetaxel) (Sanofi Aventis) accessed on 6 November 2014 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide accessed on 6 November 2014 via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
- Jones S, Holmes FA, O'Shaughnessy J, Blum JL, Vukelja SJ, McIntyre KJ. Et al. Docetaxel with cyclophosphamide is associated with an overall survival benefit compared with doxorubicin and cyclophosphamide: 7 year follow up of US Oncology Research trial 9735. *J Clin Oncol,* 2009; 27:1177-83

Written/reviewed by: Dr M Beresford (Consultant Oncologist, Royal United Hospital, Bath)

Checked by: Sarah Murdoch (Senior Oncology Pharmacist, SW Strategic Clinical Network)

Authorised by: Dr J Braybrooke (Consultant Oncologist, UHBristol NHS Trust, SW Strategic Clinical Network)

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