TAC (Docetaxel, Doxorubicin and Cyclophosphamide) (breast)

Indication

Adjuvant treatment for node positive and high risk node negative early breast cancer.

(NICE CG80)

ICD-10 codes

Codes with a prefix C50

Regimen details

Day	Drug	Dose	Route
1	Doxorubicin	50mg/m^2	IV bolus
1	Cyclophosphamide	500mg/m^2	IV bolus
1	Docetaxel	75mg/m^2	IV infusion

Cycle frequency

21 days

Number of cycles

Maximum of 6 cycles

Administration

Doxorubicin and cyclophosphamide are 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.

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

For the first cycle docetaxel should be administered 1 hour after doxorubicin and cyclophosphamide. If well tolerated it may be administered immediately after for subsequent cycles. 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

GCSF as primary prophylaxis.
Ciprofloxacin 500mg BD from days 5-14 (10 days total) may be considered following occurrence of febrile neutropenia.
Mouthwashes as per local policy
H_2 antagonist or proton-pump inhibitor if required
Loperamide if required.
Scalp cooling may be offered.

Extravasation

Doxorubicin is a vesicant (Group 5)
Cyclophosphamide is 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

ECHO or MUGA if significant cardiac history or previous anthracycline treatment.

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	≤ 1.5 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 a longer course of GCSF prophylaxis for all subsequent cycles. Reduce doses of all drugs to 80% for future cycles. Consider prophylactic ciprofloxacin (see additional supportive medication).

- **Renal impairment**

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

There is no data available on the use of doxorubicin or docetaxel in severe renal impairment. Consider dose reduction if CrCl <10mL/min (consultant decision).

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)		**Alkaline phosphatase** (xULN)	**Doxorubicin dose**	**Cyclophosphamide dose**	**Docetaxel dose**
< 1.5	and	≤ 1.5	and	≤ 2.5	100%	100%	100%
1.5 - 3	or	> 1.5	or	> 2.5	50%	100%	75%
3 - 5	or	> 3.5	and	5-10	25%		Consider dose reduction (discuss with consultant)
> 5			or	> 10	Omit	Not recommended (discuss with consultant)	Contraindicated

If bilirubin > 1.0 x ULN withhold docetaxel (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

- **Frequently occurring side effects**

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

Cardiotoxicity has been associated with anthracyclines, with adverse events being more common in patients with a prior history of coronary artery disease. Caution must be taken in patients with a history of significant cardiac disease, arrhythmias or angina pectoris.

Doxorubicin has a life time maximum cumulative dose of 450mg/m^2

References

- Martin, M., et al. Adjuvant docetaxel for node-positive breast cancer. N Engl J Med 2005; 352:2302-2313
- Summary of Product Characteristics Docetaxel (Sanofi Aventis) accessed 2 July 2014 via www.medicines.org.uk
- Summary of Product Characteristics Cyclophosphamide accessed 2 July 2014 via http://www.mhra.gov.uk/Safetyinformation/Medicinesinformation/SPCandPILs
- Summary of Product Characteristics Doxorubicin (Hospira) accessed 2 July 2014 via www.medicines.org.uk
- National Institute for Health and Clinical Excellence. Clinical Guideline 80 – Early breast cancer accessed 2 July 2014 via www.nice.org.uk

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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