

## DOCetaxel /Cyclophosphamide (TC) Therapy-21 day

### INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Adjuvant treatment of patients with high risk node-positive or node-negative early operable breast cancer.	C50	00250a	Hospital

### TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patient's individual clinical circumstances.

DOCetaxel and cyclophosphamide are administered once every 21 days for 4-6 cycles.

If radiation therapy is required, it is given following completion of chemotherapy.

Admin Order	Day	Drug	Dose	Route	Diluent & Rate
1	1	DOCetaxel	75mg/m <sup>2</sup>	IV infusion	<sup>a</sup> 250ml 0.9% NaCl over 60min
2	1	Cyclophosphamide	600mg/ m <sup>2</sup>	IV infusion <sup>b</sup>	<sup>b</sup> 250ml 0.9% NaCl over 30 min
Primary prophylaxis with G-CSF should be considered to reduce the risk of neutropenic complications (See Adverse Effects/Regimen Specific Complications)					
<sup>a</sup> 75-185mg dose use 250mL infusion bag. For doses >185mg use 500mL infusion bag <b>Use non-PVC equipment.</b>					
<sup>b</sup> Cyclophosphamide may also be administered as an IV bolus over 5-10mins . Order of administration may be reversed					

### ELIGIBILITY:

- Indications as above.
- ECOG status 0-1.
- Adequate haematological parameters (ANC > 1.5 x 10<sup>9</sup>/L, platelets > 90 x 10<sup>9</sup>/L).
- Adequate renal and hepatic function.

### EXCLUSIONS:

- Hypersensitivity to DOCetaxel, cyclophosphamide or to any of the excipients
- Severe liver impairment.
- Pregnancy or lactation.
- Grade ≥2 peripheral neuropathy.

### PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

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## TESTS:

### Baseline tests:

- FBC, Renal and Liver profile

### Regular tests:

- FBC, Renal and Liver profile\* as clinically indicated

\*See Adverse Effects/Regimen specific complications for guidelines regarding hepatic dysfunction

### Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

## DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant

### Haematological:

**Table 1: Dose modification for haematological toxicity**

ANC ( $\times 10^9/L$ )		Platelets ( $\times 10^9/L$ )	Dose
$\geq 1.5$	and	$> 90$	100%
1 – 1.49	or	70 to 90	75%
$< 1$	or	$< 70$	Delay until ANC $> 1.5$ and platelets $> 90$ then give 75% of previous cycle doses.

### Febrile Neutropenia:

**Table 2: Dose modification for febrile neutropenia**

Event	Dose reduction option
1 <sup>st</sup> episode	75% of previous cycle dose if day 1 ANC $\geq 1.5$ and platelets $\geq 100$
2 <sup>nd</sup> episode	50% of original cycle dose if day 1 ANC $\geq 1.5$ and platelets $\geq 100$
3 <sup>rd</sup> episode	Discontinue protocol.

**Note:** Post one episode of ANC 1-1.49  $\times 10^9/L$  or first episode of febrile neutropenia another consideration is the addition of G-CSF as secondary prophylaxis.

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## Renal and Hepatic Impairment:

**Table 3: Dose modification in renal and hepatic impairment**

Drug	Renal Impairment		Hepatic Impairment				
			Alkaline Phosphatase		AST and/or ALT		Serum bilirubin
DOCEtaxel	No dose reduction necessary		>2.5 ULN	and	>1.5 ULN		75mg/m <sup>2</sup>
			> 6 ULN	And /or	> 3.5 ULN (AST and ALT)	And	> ULN
							Stop treatment unless strictly indicated and should be discussed with a consultant
Cyclophosphamide	CrCl (mL/min)	Dose	Severe impairment: Clinical Decision				
	>20	100%					
	10-20	75%					
	<10	50%					

## Non-Haematological Toxicity:

**Table 4: Dose modification schedule based on adverse events**

Adverse reactions	Recommended dose modification of DOCEtaxel
Grade 3 skin reaction	Decrease dose to 60mg/m <sup>2</sup> If the patient continues to experience these reactions at 60 mg/m <sup>2</sup> , the treatment should be discontinued
Grade >2 peripheral neuropathy	
Grade 3 or 4 stomatitis	

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

DOCEtaxel: Low risk (**Refer to local policy**)

Cyclophosphamide: Moderate risk (**Refer to local policy**)

### PREMEDICATIONS:

- Dexamethasone 8 mg PO twice daily for 3 days, starting one day prior to each DOCEtaxel administration unless contraindicated. Patient must receive minimum of 3 doses pre-treatment.
- Consideration may be given, at the discretion of the prescribing consultant, to the use of a single dose of dexamethasone 20mg IV immediately before chemotherapy where patients have missed taking the oral premedication dexamethasone as recommended by the manufacturer (3,4).**

### OTHER SUPPORTIVE CARE:

- Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide.

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## ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Neutropenia:** Most frequent adverse reaction. Fever or other evidence of infection must be assessed promptly and treated appropriately. Frequent blood count monitoring should be conducted in all patients treated with DOCetaxel. DOCetaxel should be administered when the neutrophil count is  $> 1.5 \times 10^9$  cells/L.
- **Neutropenic Enterocolitis:** A number of cases of neutropenic enterocolitis have been reported in patients treated with DOCetaxel in France (5). This is a known and rare side effect of DOCetaxel which may affect up to one in 1,000 people.
- **Hypersensitivity Reactions:** Patients should be observed closely for hypersensitivity reactions especially during the first and second infusions of DOCetaxel. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of DOCetaxel, thus facilities for the treatment of hypotension and bronchospasm should be available. If hypersensitivity reactions occur, minor symptoms such as flushing or localized cutaneous reactions do not require interruption of therapy. However, severe reactions, such as severe 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.
- **Fluid Retention:** Dexamethasone premedication must be given to reduce the incidence and severity of fluid retention with DOCetaxel. It can also reduce the severity of the hypersensitivity reaction.
- **Extravasation:** DOCetaxel causes pain and tissue necrosis if extravasated. (Refer to local extravasation guidelines).
- **Hepatic Dysfunction:** DOCetaxel undergoes hepatic metabolism. Hepatic dysfunction (particularly elevated AST) may lead to increased toxicity and usually requires a dose reduction.
- **SIADH** (syndrome of inappropriate secretion of antidiuretic hormone): may occur in patients receiving cyclophosphamide, resulting in hyponatremia, dizziness, confusion or agitation, unusual tiredness or weakness. This syndrome is more common with doses  $>50$  mg/kg and may be aggravated by administration of large volumes of fluids to prevent hemorrhagic cystitis. The condition is self-limiting although diuretic therapy may be helpful in the situation when the patient has stopped urinating (especially if this occurs during the first 24 hours of cyclophosphamide therapy). Susceptible patients should be monitored for cardiac decompensation.

## DRUG INTERACTIONS:

- Risk of drug interactions causing increased concentrations of DOCetaxel with CYP3A4 inhibitors. These drugs also decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of DOCetaxel with CYP3A4 inducers. These drugs also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Cyclophosphamide inhibits cholinesterase metabolism of suxamethonium which may prolong its neuromuscular blocking effect.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	29/04/2015		Dr Maccon Keane
2	30/05/2015	Modification of premedication regimen	Dr Maccon Keane
3	28/06/2017	Updated with new NCCP template, clarified title and dosing in renal and hepatic impairment and admin order Clarified use of G-CSF and updated re neutropenic enterocolitis	Prof Maccon Keane
4	16/01/2019	Updated dose modification of docetaxel in hepatic impairment table Standardised administration of docetaxel and cyclophosphamide	Prof Maccon Keane
5	06/11/2019	Update of route of administration for cyclophosphamide.	Prof Maccon Keane
6	08/01/2020	Update of cyclophosphamide dose modifications in hepatic impairment	Prof Maccon Keane
7	10/02/2021	Amended eligibility and emetogenic potential	Prof Maccon Keane

Comments and feedback welcome at [oncologydrugs@cancercontrol.ie](mailto:oncologydrugs@cancercontrol.ie).

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