DOXOrubicin, and Cyclophosphamide (AC 60/600)Therapy - 21 day

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement status
Adjuvant treatment of high risk node negative or node positive breast cancer.	C50	00252a	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 patients individual clinical circumstances.

DOXOrubicin and cyclophosphamide are administered once every 21 days for four cycles (one cycle = 21 days).
If radiation therapy is required, it is given following completion of chemotherapy.

Order of Admin	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOXOrubicin	60mg/m^2	IV push	Slow IV push over 15min	Every 21 days for up to 4 cycles
2	1	Cyclophosphamide	600mg/m^2	IV infusion*	250ml 0.9% sodium chloride over 30min	Every 21 days for up to 4 cycles
* Cyclophosphamide may also be administered as an IV bolus over 5-10mins						
Lifetime cumulative dose of DOXOrubicin is 450mg/m^2 **In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors outlined below[i] and to the age of the patient.**						

Facilities to treat anaphylaxis MUST be present when the chemotherapy is administered.

ELIGIBILITY:

- Indications as above.
- ECOG status 0-2.

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cyclophosphamide or any of the excipients.
- Congestive heart failure (LVEF < 50%) or other significant heart disease.

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile.
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated

Regular tests:

- FBC, renal and liver profile
- If clinically indicated creatinine, MUGA scan or echocardiogram

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 modifications for cycles of DOXOrubicin and cyclophosphamide

ANC (x10^9/L)	Platelets (x10^9/L)	Dose (Both Drugs)
≥ 1.5	> 90	100%
1 -1.49	70 to 90	*75%
< 1	< 70	Delay

*May consider using G-CSF for neutrophil support rather than dose reduction

Renal and Hepatic Impairment:

Table 2: Dose modification of DOXOrubicin and Cyclophosphamide in Renal and hepatic impairment

Drug	Renal Impairment		Hepatic Impairment	
DOXOrubicin	No dose reduction required. Clinical decision in severe impairment		**Serum Bilirubin (micromol/L)**	**Dose**
			20-51	50%
			51-85	25%
			>85	Omit
			If AST 2-3 x normal give 75% If AST > 3 x ULN give 50%	
Cyclophosphamide	**CrCl (mL/min)**	**Dose**	Severe impairment. Clinical Decision	
	>20	100%		
	10-20	75%		
	<10	50%		

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOXOrubicin: High **(Refer to local policy)**
Cyclophosphamide: Moderate **(Refer to local policy)**

PREMEDICATIONS: None usually required

OTHER SUPPORTIVE CARE:

Prophylactic G-CSF may be used to mitigate the risk of haematological toxicities.
Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cyclophosphamide.

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**: Fever or other evidence of infection must be assessed promptly and treated appropriately.
- **Extravasation**: DOXOrubicin may cause pain and tissue necrosis if extravasated. **(Refer to local extravasation guidelines).**
- **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

DRUG INTERACTIONS:

- CYP3A inhibitors decrease the conversion of cyclophosphamide to both its active and inactive metabolites. Patients should also be counselled with regard to consumption of grapefruit juice.
- CYP3A inducers may also increase the conversion of cyclophosphamide to both its active and inactive metabolites.
- Concurrent administration of calcium channel blockers with DOXOrubicin should be avoided as they may decrease the clearance of DOXOrubicin.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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2. Fisher B, Brown AM, Dimitrov NV et al. Two months of doxorubicin-cyclophosphamide with and without interval reinduction therapy compared with 6 months of cyclophosphamide, methotrexate and fluorouracil in positive-node breast cancer patients with tamoxifen-nonresponsive tumors: results from the National Surgical Adjuvant Breast and Bowel Project B-15. J Clin Oncol 1990;8(9):1483-96.

3. Doxorubicin 2mg/ml Concentrate for Solution for Infusion. Summary of Product Characteristics. Accessed April 2021. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2315-083-001_26022020112618.pdf
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5. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
6. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009; North London Cancer Network.
7. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V3 2021. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf

Version	Date	Amendment	Approved By
1	29/04/2015		Dr Maccon Keane
2	14/06/2017	Updated title, clarified administration order and dosing in renal and hepatic impairment, applied new NCCP regimen template	Prof Maccon Keane
3	19/06/2019	Standardisation of treatment table for NCIS.	Prof Maccon Keane
4	06/11/2019	Standardisation of treatment table	Prof Maccon Keane
5	08/01/2020	Update of cyclophosphamide dose modifications in hepatic impairment	Prof Maccon Keane
6	12/05/2021	Reviewed. Amended emetogenic potential.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] Cardiotoxicity is a risk associated with anthracycline therapy that may be manifested by early (acute) or late (delayed) effects.
Risk factors for developing anthracycline-induced cardiotoxicity include:
• high cumulative dose, previous therapy with other anthracyclines or anthracenediones
• prior or concomitant radiotherapy to the mediastinal/pericardial area
• pre-existing heart disease
• concomitant use of other potentially cardiotoxic drugs
In establishing the maximal cumulative dose of an anthracycline, consideration should be given to the risk factors above and to the age of the patient