Dose Dense DOXOrubicin, cycloPHOSphamide (AC 60/600) 14 day followed by PACLitaxel (175) 14 day Therapy (DD AC-T)

Note: There is an option for DOXOrubicin, cycloPHOSphamide followed by weekly PACLitaxel (AC–T) therapy described in regimen NCCP00260.

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Adjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer.	C50	00278a	Hospital
Neoadjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer.	C50	00278b	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 14 days for four cycles (one cycle = 14 days) followed by PACLitaxel once every 14 days for 4 cycles (8weeks) to start **14 days after** final cycle of DOXOrubicin and cycloPHOSphamide.
G-CSF support (using standard or pegylated form) is required with all cycles.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Cycle 1-4:

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOXOrubicin	60mg/ m^2	IV push	N/A	Every 14 days for 4 cycles
2	1	cycloPHOSphamide	600mg/m^2	IV infusion*	250ml 0.9% NaCl over 30min	Every 14 days for 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.**						

Cycle 5-8:

Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	PACLitaxel	175mg/m^2	IV infusion	500ml 0.9% NaCl over 3hr	Every 14 days from cycle 5 for 4 cycles
PACLitaxel must be supplied in non-PVC containers and administered using non-PVC giving sets and through an in-line 0.22 µm filter with a microporous membrane.					
PACLitaxel should be diluted to a concentration of 0.3-1.2mg/ml.					

ELIGIBILITY:

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

EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cycloPHOSphamide, PACLitaxel or any of the excipients.
- Congestive heart failure (LVEF <50%) or other significant heart disease.
- Baseline neutrophil count $<1.5x10^9/L$
- Severe hepatic impairment
- Breast feeding

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 prior to each cycle
- 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 haematological toxicity

ANC ($x10^9$/L)		Platelets ($x10^9$/L)	Dose (All Drugs)
≥ 1	and	> 100	100%
<1	and	≥100	Delay for 1 week (or longer if needed), then give 100% dose if ANC>1 and platelets ≥100.
≥ 1	and	< 100	Delay for 1 week (or longer if needed), then give 100% dose if ANC>1.0 and platelets ≥100. Dose reduce to 75% after a second delay.
Febrile Neutropenia: 75% of dose for current and subsequent cycles.			

Renal and Hepatic Impairment:

Table 2: Dose modification of DOXOrubicin, cycloPHOSphamide and PACLitaxel 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%		
PACLitaxel	No dose reductions necessary		See Table 3 below	

Table 3: Dose modification of PACLitaxel in hepatic Impairment

ALT		Total bilirubin	Dose of PACLitaxel
< 10xULN	and	≤ 1.25xULN	175mg/m^2
< 10xULN	and	1.26-2xULN	135mg/m^2
< 10xULN	and	2.01-5xULN	90mg/m^2
≥10xULN	and/or	>5xULN	Not recommended

Non-Haematological Toxicity:

Table 4: Dose modification schedule for PACLitaxel based on adverse events

Adverse reactions	Recommended dose modification
Grade 2 motor or sensory neuropathy	Dose reduction or delay in treatment may be required.
≥ Grade 3 reaction	Discontinue

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

DOXOrubicin cycloPHOSphamide cycles: High **(Refer to local policy).**
PACLitaxel: Low **(Refer to local policy).**

PREMEDICATIONS:

- **DOXOrubicin cycloPHOSphamide cycles:** None usually required

- **PACLitaxel cycles:** All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to first dose of PACLitaxel treatment.
- The H_2 antagonist, famotidine, can potentially be omitted from the pre-medication requirements for PACLitaxel but the risk of hypersensitivity with this approach is unknown.
    - Caution is advised particularly for patients receiving PACLitaxel every 3 weeks. It is recommended that if famotidine is omitted that patients are monitored closely for any signs of hypersensitivity. Any hypersensitivity should be managed as per local policy.
    - Where a patient experiences hypersensitivity, consider the use of alternative H_2 antagonists **(Refer to local policy).**

Table 5: Suggested premedications prior to treatment with PACLitaxel

Drug	Dose	Administration prior to PACLitaxel
dexAMETHasone	20mg oral or IV[a,b]	For oral administration: approximately 6 and 12 hours or for IV administration: 30 minutes
Chlorphenamine	10mg IV	30 minutes
Famotidine[c]	20mg IV	30 minutes
[a]Dose of dexAMETHasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance.		
[b]If aprepitant is added to the anti-emetic regimen, consideration should be given to reducing the dose of dexAMETHasone to 12mg on the day of treatment.		
[c]Dose of famotidine may be omitted in the absence of hypersensitivity reaction according to consultant guidance.		

OTHER SUPPORTIVE CARE:

- G-CSF (**Refer to local policy**)
- Patients should have an increased fluid intake of 2-3 litres on day 1 to prevent haemorrhagic cystitis associated with cycloPHOSphamide.
- Myalgias and arthralgias may occur with PACLitaxel. Analgesic cover should be considered.

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 and PACLitaxel 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.

PACLitaxel

- **Hypersensitivity:** Severe hypersensitivity reactions characterised by dyspnoea and hypotension requiring treatment, angioedema and generalised urticaria have occurred in <1% of patients receiving PACLitaxel after adequate premedication. In the case of severe hypersensitivity reactions, PACLitaxel infusion should be discontinued immediately, symptomatic therapy should be initiated and the patient should not be re-challenged with the drug**.**
- **Peripheral neuropathy:** Occurs frequently but the development of severe symptoms is rare.
- **Arthralgia/myalgia:** May be severe in some patients; however, there is no consistent correlation between cumulative dose and infusion duration of PACLitaxel and frequency or severity of the arthralgia/myalgia. Symptoms are usually transient, occurring within 2 or 3 days after PACLitaxel administration, and resolving within days.
- **Cardiac conduction abnormalities:** If patients develop significant conduction abnormalities during PACLitaxel administration, appropriate therapy should be administered and continuous cardiac monitoring should be performed during subsequent therapy with PACLitaxel. Hypotension, hypertension, and bradycardia have been observed during PACLitaxel administration; patients are usually asymptomatic and generally do not require treatment. Frequent vital sign monitoring, particularly during the first hour of PACLitaxel infusion, is recommended.
- **Hepatic Dysfunction:** Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.

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.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A inhibitors. Patients should also be counselled with regard to consumption of grapefruit juice.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A inducers.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	15/11/2015		Dr Maccon Keane
2	15/11/2017	Updated title, clarified administration order and dosing in renal and hepatic impairment, applied new NCCP regimen template	Prof Maccon Keane
3	07/02/2018	Updated premedication regimen	Prof Maccon Keane
4	06/11/2019	Reviewed. Standardisation of treatment table and premedications. Update of adverse events.	Prof Maccon Keane
5	08/01/2020	Update of cyclophosphamide dose modifications in hepatic impairment.	Prof Maccon Keane
6	12/06/2022	Updated premedication regimen. Regimen review.	Prof Maccon Keane

7	22/09/2023	Updated premedication section for PACLItaxel.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[ii]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