# Dose Dense DOXOrubicin, cycloPHOSphamide (AC 60/600) 14 day followed by PACLitaxel (80) 7 day Therapy (DD AC-T)

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | Reimbursement Status |
|---|---|---|---|
| Adjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer. | C50 | 00485a | Hospital |
| Neoadjuvant Treatment of High Risk Node Negative or Node Positive Breast Cancer. | C50 | 00485b | 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.*

Dose dense DOXOrubicin and cycloPHOSphamide are administered once every 14 days for four cycles (one cycle = 14 days) followed by PACLitaxel once every 7 days for 12 weeks to start **14 days after** final cycle of dose dense DOXOrubicin and cycloPHOSphamide.
G-CSF support (using standard or pegylated form) is required with all cycles of dose dense DOXOrubicin and cycloPHOSphamide.

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

**Cycle 1-4 (Dose Dense):**

| 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% sodium chloride over 30 min | 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/$m^2$<br>**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, 8 and 15 | PACLitaxel | 80mg/$m^2$ | IV infusion | 250ml 0.9% sodium chloride over 1hr | Every 21 days for cycle 5-8 |
| 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 < 1.5 x $10^9$/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 cycles of DOXOrubicin and cycloPHOSphamide only**

| ANC (x$10^9$/L) | | Platelets (x$10^9$/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.<br>Dose reduce to 75% after a second delay. |
| Febrile Neutropenia: 75% of dose for current and subsequent cycles. | | | |

**Table 2: Dose modifications for PACLitaxel for haematological toxicity**

| ANC (x$10^9$/L) | | Platelets | Dose | Dose after neutropenic sepsis |
|---|---|---|---|---|
| ≥ 1.5 | and | > 90 | 80mg/m$^2$ | 65mg/m$^2$ |
| *1-1.49 | or | 70-90 | 65mg/m$^2$ | 50mg/m$^2$ |
| < 1 | or | < 70 | Delay and reduce next dose to 65mg/m$^2$ or add G-CSF | Delay |
| Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment. | | | | |

*** If ANC 1 to less than 1.5 and patient fit and well can consider full dose of 80 mg/m$^2$ at discretion of prescribing Consultant**

### Renal and Hepatic Impairment:

**Table 3: 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%<br>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 4 below | |

**Table 4: Dose modification of PACLitaxel in hepatic Impairment**

| ALT | | Total bilirubin | Dose of PACLitaxel |
|---|---|---|---|
| < 10xULN | and | ≤ 1.25xULN | 80mg/m$^2$ |
| < 10xULN | and | 1.26-2xULN | 60mg/m$^2$ |
| < 10xULN | and | 2.01-5xULN | 40mg/m$^2$ |
| ≥10xULN | and/or | >5xULN | Not recommended |

### Non-Haematological Toxicity:

**Table 5: Dose modification schedule for PACLitaxel based on adverse events**

| Adverse reactions | Recommended dose modification |
|---|---|
| Grade 2 motor or sensory neuropathy | Decrease dose by 10mg/m$^2$. |
| All other grade 2 non-haematological toxicity | Hold treatment until toxicity resolves to ≤ grade 1. Decrease subsequent doses by 10mg/m$^2$. |
| ≥ Grade 3 reaction | Discontinue |

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

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

## PREMEDICATIONS:

**Dose dense DOXOrubicin/cycloPHOSphamide cycles**: None usually required. **(See other supportive care for g-csf support)**

**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 6: Suggested premedications prior to treatment with PACLitaxel**

| Day of treatment | Drug | Dose | Administration prior to PACLitaxel |
|---|---|---|---|
| Day 1 | dexAMETHasone[a] | 8mg IV | 30 minutes |
| Day 1 | Chlorphenamine | 10mg IV | 30 minutes |
| Day 1 | Famotidine | 20mg IV | 30 minutes |
| Day 8[b] and thereafter | dexAMETHasone[a] | None | |
| Day 8 and thereafter | Chlorphenamine | 10mg IV | 30 minutes |
| Day 8 and thereafter | Famotidine[c] | 20mg IV | 30 minutes |
| [a]Dose of dexAMETHasone may be altered, in the event of hypersensitivity reaction, to 20 mg of dexAMETHasone orally 12 hr and 6 hr prior to re-challenge with PACLitaxel according to consultant guidance. | | | |
| [b]Dose of dexAMETHasone may be added from day 8 if increased risk or previous hypersensitivity reaction according to consultant guidance. | | | |
| [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.*

Please refer to NCCP regimen 00252 for detailed information on the adverse effects associated with DOXOrubicin cycloPHOSphamide therapy and NCCP regimen 00226 for information relating to weekly PACLitaxel therapy

## 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.

## REFERENCES:


1. Citron ML, Berry DA, Cirrincione C. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol 2003; 21 (8): 1431-1439.
2. Sparano JA, Wang M, Martino S et al. Weekly Paclitaxel in the Adjuvant Treatment of Breast Cancer: Results of Intergroup Trial E1199. N Engl J Med. 2008 April 17; 358(16): 1663-1671.
3. Morris PG, Dickler M et al. Dose-Dense Adjuvant Doxorubicin and Cyclophosphamide Is Not Associated With Frequent Short-Term Changes in Left Ventricular Ejection Fraction. J Clin Oncol 2009;27 (36):6117-6123.
4. Dosage Adjustment for Cytotoxics in Renal Impairment January 2009; North London Cancer Network.
5. Dosage Adjustment for Cytotoxics in Hepatic Impairment January 2009;North London Cancer Network.
6. Quock J et al. Premedication strategy for weekly paclitaxel. Cancer investigation. Volume 20, 2002 issue 5-6
7. Uptodate infusion reactions to systemic chemotherapy available at https://www.uptodate.com/contents/infusion-reactions-to-systemic-chemotherapy#H37
8. Cyclophosphamide (Endoxana) 1000mg Injection Powder for Solution for Injection. Summary of Product Characteristics Last updated:December 2018. Accessed May 2022. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA2299-027-002_21122018112109.pdf
9. DOXOrubicin HCl 50mg Powder for Solution for Injection. Summary of Product Characteristics. Accessed Nov 2022 .Available at http://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0437-026-002_03032016152104.pdf
10. PACLitaxel. Summary of Product Characteristics. Accessed May 2022. Available at: https://www.hpra.ie/img/uploaded/swedocuments/Licence_PA1963-010-001_18022019145902.pdf

| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 01/06/2018 | | Prof Maccon Keane |
| 2 | 23/10/2019 | Standardisation of treatment table and table for suggested premedications prior to treatment with PACLitaxel | Prof Maccon Keane |
| 3 | 31/12/2019 | Updated recommendation for hepatic impairment | Prof Maccon Keane |
| 4 | 27/05/2020 | Regimen reviewed | Prof Maccon Keane |
| 5 | 22/09/2023 | Updated premedications table. | 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