# Dose Dense DOXOrubicin, Cyclophosphamide (AC 60/600) 14 day followed by weekly PACLitaxel (80) and weekly Trastuzumab Therapy (AC-TH)

**Note: There is an option for Dose Dense DOXOrubicin, cyclophosphamide – PACLitaxel (14 days) and trastuzumab therapy described in protocol NCCP- 00316.**

## INDICATIONS FOR USE:

| INDICATION | ICD10 | Regimen Code | *Reimbursement Indicator |
|---|---|---|---|
| Adjuvant Treatment of HER2 positive, High Risk Node Negative or Node Positive Breast Cancer. | C50 | 00433a | |
| Neoadjuvant Treatment of HER2 positive, High Risk Node Negative or Node Positive Breast Cancer. | C50 | 00433b | |

*If a reimbursement indicator (e.g. ODMS, CDS[i]) is not defined, the drug and its detailed indication have not been assessed through the formal HSE reimbursement process.*

## 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 and trastuzumab once every 7 days for 12 weeks.
Following completion of the 12 weeks, trastuzumab 6mg/kg (ref NCCP protocol 00200 Trastuzumab monotherapy-21days) every 21 days to complete one year of trastuzumab therapy may be given.

Facilities to treat anaphylaxis MUST be present when trastuzumab is administered

**G-CSF support (using standard or pegylated form) is required with all cycles.**

**4 Cycles of DOXOrubicin/Cyclophosphamide (Cycles 1-4 of treatment)**

| Order of Admin. | Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|---|
| 1 | 1 | DOXOrubicin | 60mg/ $m^2$ | IV push | N/A | Repeat every 14 days for cycle 1-4 |
| 2 | 1 | Cyclophosphamide | 600mg/$m^2$ | IV infusion* | 100 to 250ml 0.9% sodium chloride over 20min to 1 hr | Repeat every 14 days for cycle 1-4 |
| * 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[ii] and to the age of the patient.** | | | | | | |

**4 Cycles of PACLitaxel/Trastuzumab (Cycles 5-8 of treatment)**

| Day | Drug | Dose | Route | Diluent & Rate | Cycle |
|---|---|---|---|---|---|
| 1,8, 15 | PACLitaxel | 80mg/m$^2$ | IV infusion | 250 to 500ml 0.9% sodium chloride or glucose 5% over 1hr | Repeat every 21 days for cycle 5-8 |
| 1 | Trastuzumab | 4mg/kg | IV infusion Observe post infusion* | 250ml 0.9% sodium chloride over 90min | 5, day 1 **only** |
| 8, 15 | Trastuzumab | 2mg/kg | IV infusion Observe post infusion* | If no adverse reactions use250ml 0.9% sodium chloride over 30min | 5, day 8 and day 15 only |
| 1, 8, 15 | Trastuzumab | 2mg/kg | IV infusion Observe post infusion* | If no adverse reactions use250ml 0.9% sodium chloride over 30min | Repeat every 21 days for cycle 6-8 |
| 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. | | | | | |
| *Recommended Observation period: Patients should be observed for at least six hours after the start of the first infusion and for two hours after the start of the subsequent infusions for symptoms like fever and chills or other infusion-related symptoms. Any deviation should be noted in local policies. | | | | | |
| ** Trastuzumab is incompatible with glucose solution | | | | | |

Following completion of the 12 weeks of PACLitaxel/trastuzumab treatment, trastuzumab 6mg/kg (Reference NCCP protocol 00200 Trastuzumab monotherapy-21 days) every 21 days to complete one year of trastuzumab therapy should be given.

## ELIGIBILTY:

- Indications as above.
- HER2 overexpression or HER2 gene amplification as determined by an accurate and validated assay
- ECOG status 0-2.

## EXCLUSIONS:

- Hypersensitivity to DOXOrubicin, cyclophosphamide, PACLitaxel, trastuzumab or any of the excipients.
- Congestive heart failure (LVEF < 50%) or other or other clinically significant cardiac disease (history of symptomatic ventricular arrhythmias, congestive heart failure or myocardial infarction within previous 12 months).
- 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, liver and renal profile
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated

**Regular tests**:

- FBC, liver and renal profile
- Cardiac function (MUGA or ECHO) every 12 weeks. Where there are signs of cardiac impairment four to eight weekly checks may be more appropriate.

**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
- If the patient misses a dose of trastuzumab by one week or less, then the usual maintenance dose of 2mg/kg should be given as soon as possible. Do not wait until the next planned cycle. Subsequent maintenance doses should then be given according to the previous schedule.
- If the patient misses a dose of trastuzumab by more than one week, a re-loading dose of trastuzumab (4 mg/kg) should be given over approximately 90 minutes, at the discretion of the clinician. Subsequent trastuzumab maintenance doses (2 mg/kg) should then be given weekly from that point.

**Haematological:**

**Table 1: Dose modifications for cycles of DOXOrubicin cyclophosphamide only**

| ANC (x$10^9$/L) | | Platelets (x$10^9$/L) | Dose (Both Drugs) |
|---|---|---|---|
| ≥ 1.0 | and | ≥ 100 | 100% |
| <1.0 | and | ≥100 | Delay for 1 week (or longer if needed), then give 100% dose if ANC > 1.0 and platelets ≥ 100. |
| ≥ 1.0 | 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

**Table 2: For cycles of PACLitaxel only**

| 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 |

## 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 | Not recommended in patients with a bilirubin >17micromolmol/L or serum transaminases or ALP more than 2-3 x upper limit of normal. Clinical Decision | |
| | >20 | 100% | | |
| | 10-20 | 75% | | |
| | <10 | 50% | | |
| PACLitaxel | No dose reductions necessary | | See Table 4 below | |
| Trastuzumab | Probably no dose reduction necessary | | Probably no dose reduction necessary | |

**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 | Discontinue | 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 | |

**Table 6: Trastuzumab dose modification schedule based on adverse events**

| Adverse reactions | Discontinue | Recommended dose modification |
|---|---|---|
| LVEF drops 10 ejection fraction points from baseline and to below 50% | | Withhold treatment. Repeat LVEF after 3 weeks. No improvement or further decline, consider discontinuation. Discuss with consultant and refer to cardiologist. |
| Symptomatic heart failure | Discontinue | |
| NCI-CTCAE Grade 4 hypersensitivity reactions | Discontinue | |
| Haematological | | Treatment may continue during periods of reversible, chemotherapy-induced myelosuppression. Monitor carefully for any complications of neutropenia. |

## SUPPORTIVE CARE:

### EMETOGENIC POTENTIAL:

DOXOrubicin cyclophosphamide (AC) cycles: High **(Refer to local policy).**
PACLitaxel and trastuzumab (TH): Low **(Refer to local policy)**

### PREMEDICATIONS:

DOXOrubicin cyclophosphamide (AC) cycles: None usually required

All patients must be premedicated with corticosteroids, antihistamines, and $H_2$ antagonists prior to PACLitaxel treatment. Table 7 outlines suggested premedications prior to treatment with PACLitaxel

**Table 7: Suggested predmedications prior to treatment with PACLitaxel**

| Drug | Dose | Administration prior to PACLitaxel |
|---|---|---|
| Dexamethasone | 10mg IV[a] | 30 to 60 minutes |
| Diphenhydramine [b] | 50mg IV | 30 to 60 minutes |
| Cimetidine or ranitidine | 300mg IV<br>50mg IV | 30 to 60 minutes |
| [a]Dose of dexamethasone may be reduced or omitted in the absence of hypersensitivity reaction according to consultant guidance. | | |
| [b] or an equivalent antihistamine e.g. chlorphenamine | | |

## OTHER SUPPORTIVE CARE:

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 Protocol 00252 for information on the adverse effects associated with DOXOrubicin cyclophosphamide therapy
- NCCP protocol 00226 for information on the adverse effects associated with weekly PACLitaxel therapy
- NCCP protocol 00201 for information on the adverse effects associated with trastuzumab 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 with CYP3A inhibitors may cause increased concentrations of PACLitaxel. Patients should also be counselled with regard to consumption of grapefruit juice.

- Risk of drug interactions with CYP3A inducers may cause decreased concentrations of PACLitaxel.
- Current drug interaction databases should be consulted for more information.

## ATC CODE:

| | |
|---|---|
| DOXOrubicin | L01DB01 |
| Cyclophosphamide | L01AA01 |
| PACLitaxel | L01CD01 |
| Trastuzumab | L01XC03 |

## REFERENCES:


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3. Dang et al: The safety of dose dense DOXOrubicin and cyclophosphamide followed by PACLitaxel with trastuzumab in the HER-2/neu over-expressed/ amplified breast cancer. J Clin Oncol 2008; 26 (8): 1216-22.
4. 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
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| Version | Date | Amendment | Approved By |
|---|---|---|---|
| 1 | 23/10/2017 | | Prof Maccon Keane |
| 2 | | | |

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.

[i] ODMS – Oncology Drug Management System
CDS – Community Drug Schemes (CDS) including the High Tech arrangements of the PCRS community drug schemes
Further details on the Cancer Drug Management Programme is available at;
http://www.hse.ie/eng/services/list/5/cancer/profinfo/medonc/cdmp/

[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