Weekly CARBOplatin (AUC 2) and PACLitaxel 80mg/m^2 followed by Dose Dense DOXOrubicin cycloPHOSphamide Therapy - Triple Negative Breast Cancer Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Neoadjuvant treatment of triple negative breast carcinoma	C50	00734a	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.

CARBOplatin and PACLitaxel are administered on days 1, 8 and 15 of a 21 day cycle for 4 cycles or until disease progression or unacceptable toxicity develops.

This is then followed by DOXOrubicin and cycloPHOSphamide administered once every 14 days for 4 cycles (one cycle = 14 days).

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

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

4 Cycles of PACLitaxel/CARBOplatin (Cycles 1-4 of treatment)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1,8,15	PACLitaxel	80mg/m^2	IV infusion	250ml 0.9% NaCL over 60 min	Repeat every 21 days for cycles 1 - 4
2	1,8,15	CARBOplatin	AUC 2	IV infusion	250ml glucose 5% over 30 min	Repeat every 21 days for cycles 1 - 4
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.						

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4 Cycles of DOXOrubicin/cycloPHOSphamide (Cycles 5-8 of treatment)

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	DOXOrubicin[a]	60mg/ m^2	IV push	N/A	Repeat every 14 days for cycles 5 - 8
2	1	cycloPHOSphamide	600mg/m^2	IV infusion[b]	250ml 0.9% NaCl over 30 min	Repeat every 14 days for cycles 5 - 8
[a] cycloPHOSphamide may also be administered as an IV bolus over 5-10mins.						
[b] 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.						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- Estimation of GFR (eGFR) can be done by using the Wright formula or using the Cockcroft and Gault formula to measure creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.
- For obese patients and those with a low serum creatinine, for example due to low body weight or post-operative asthenia, the formulae may not give accurate results and measured GFR is recommended.
  - Where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available, the use of the adjusted ideal body weight for Cockcroft and Gault may be considered.
  - Where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.
- These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

GFR (ml/min) = (6230 - 32.8 x Age) x BSA x (1 - 0.23 x Sex)

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SCr (micromol/min)

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \textit{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{\text{S} \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serum creatinine (micromol/L)}}$$

S = 1.04 for females and 1.23 for males

ELIGIBILITY:

- Indications as above
- Triple negative breast cancer
- ECOG status 0-2
- Adequate organ function; ANC > 1.5 x10^9/L, platelets 75 x10^9/L

EXCLUSIONS:

- Hypersensitivity to CARBOplatin, PACLitaxel, DOXOrubicin, cycloPHOSphamide or any of the excipients
- Congestive heart failure (LVEF < 50%) or other significant heart disease
- Disease progression while receiving platinum based chemotherapy
- Pregnancy or lactation
- Severe hepatic impairment (PACLitaxel)
- Baseline neutrophil count < 1.5 x 10^9/L

PRESCRIPTIVE AUTHORITY:

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

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TESTS:

Baseline tests:

- FBC, liver and kidney profile
- Audiometry and creatinine clearance as clinically indicated
- ECG
- MUGA or ECHO (LVEF > 50% to administer DOXOrubicin) if >65 years or if clinically indicated (e.g. smoking history, hypertension)
- Isotope GFR measurement (preferred) or GFR / CrCl estimation

Regular tests:

- FBC weekly during treatment
- Liver and kidney profiles weekly
- Assessment of peripheral neuropathy status before each cycle (PACLitaxel only)
- 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 of PACLitaxel and CARBOplatin for haematological toxicity

ANC (x 10^9/L) Pretreatment blood test	
≥1.0	100% dose
0.5 to < 1.0	Delay treatment until recovery
< 0.5	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Febrile neutropenia or previous delay for myelosuppression	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles
Prolonged recovery greater than two weeks delay or 3rd delay for myelosuppression	Delay treatment until recovery, consider reducing PACLitaxel and CARBOplatin by 50% for subsequent cycles or cease
Platelets (x 10^9/L) Pretreatment blood test	
≥ 100	100% dose
75 to < 100	Clinician's discretion; continue treatment if patient is clinically well.
50 to < 75	Delay treatment until recovery
< 50	Delay treatment until recovery and consider reducing PACLitaxel and CARBOplatin by 25% for subsequent cycles

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Table 2: Dose modification of DOXOrubicin and cycloPHOSphamide for haematological toxicity

ANC (x 10^9 /L)		Platelet count (x 10^9 /L)	Dose
≥ 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.

Renal and Hepatic Impairment:

Table 3: Dose modification in renal and hepatic impairment

<table>
<tr><th>Drug</th><th colspan="2">Renal Impairment</th><th colspan="4">Hepatic Impairment</th></tr>
<tr><td>CARBOplatin</td><td colspan="2">See note below*</td><td colspan="4">No dose modification required</td></tr>
<tr><td rowspan="5">PACLitaxel</td><td colspan="2" rowspan="5">Renal impairment: no need for dose adjustment is expected.
Haemodialysis: no need for dose adjustment is expected.</td><td>ALT</td><td></td><td>Total Bilirubin</td><td>Dose</td></tr>
<tr><td>< 10xULN</td><td>and</td><td>≤ 1.25xULN</td><td>80mg/m^2</td></tr>
<tr><td>< 10xULN</td><td>and</td><td>1.26-2xULN</td><td>60mg/m^2</td></tr>
<tr><td>< 10xULN</td><td>and</td><td>2.01-5xULN</td><td>40mg/m^2</td></tr>
<tr><td>≥10xULN</td><td>and /or</td><td>>5xULN</td><td>Not recommended</td></tr>
<tr><td rowspan="4">cycloPHOSphamide</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="4" rowspan="4">Mild and moderate: no need for dose adjustment is expected.
Severe: not recommended, due to risk of reduced efficacy.</td></tr>
<tr><td>≥ 30</td><td>100%</td></tr>
<tr><td>10-29</td><td>Consider 75% of the original dose.</td></tr>
<tr><td>< 10</td><td>Not recommended. If unavoidable consider 50% of the original dose.</td></tr>
<tr><td></td><td>Haemodialysis</td><td>Not recommended. If unavoidable consider 50% of the original dose.</td><td colspan="4"></td></tr>
<tr><td rowspan="4">DOXOrubicin</td><td>CrCl (ml/min)</td><td>Dose</td><td colspan="2">Serum Bilirubin (micromol/L)</td><td>Dose</td></tr>
<tr><td></td><td></td><td colspan="2">20-50</td><td>50%</td></tr>
<tr><td>>10</td><td>No dose adjustment is needed.</td><td colspan="2">> 51-86</td><td>25%</td></tr>
<tr><td><10</td><td>No need for dose adjustment is expected.</td><td colspan="2">> 86 or Child Pugh C</td><td>Not recommended</td></tr>
<tr><td></td><td>Haemodialysis</td><td>75% of the original dose may be considered.</td><td colspan="3"></td></tr>
</table>

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***Renal Dysfunction and CARBOplatin**

- Patients with creatinine clearance values of <60ml/min are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be adjusted as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to re-measuring the GFR or to recalculating using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 4: Dose Modification of PACLitaxel for Adverse Events

Adverse reactions	Recommended dose modification
Grade ≥2 motor or sensory neuropathy First Occurrence Persistent Grade ≥2 or 2nd occurrence	Decrease dose of PACLitaxel by 10mg/m^2. Decrease dose of PACLitaxel by a further 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

Patients who cannot tolerate treatment after 2 dose reductions or require a treatment delay of greater than 2 weeks, should discontinue treatment

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

CARBOplatin: Moderate **(Refer to local policy)**
PACLitaxel: Low **(Refer to local policy)**
cycloPHOSphamide: Moderate **(Refer to local policy)**
DOXOrubicin: High **(Refer to local policy)**

PREMEDICATIONS:

- All patients must be premedicated with corticosteroids, antihistamines, and H_2 antagonists prior to 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).**

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Table 5 outlines the suggested premedications prior to treatment with PACLitaxel.

Table 5: 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:

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.
- **Hypersensitivity**: Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin. 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.
- **Extravasation**: PACLitaxel causes pain and tissue necrosis if extravasated. DOXOrubicin may cause pain and tissue necrosis if extravasated **(Refer to local policy).**

CARBOplatin:

- **Neurotoxicity and ototoxicity:** Neurological evaluation and an assessment of hearing should be performed on a regular basis, especially in patients receiving high dose CARBOplatin. Neurotoxicity, such as parasthesia, decreased deep tendon reflexes, and ototoxicity are more likely seen in patients previously treated with cisplatin, other platinum treatments and other ototoxic agents. Frequency of neurologic toxicity is also increased in patients older than 65 years.

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PACLitaxel:

- **Peripheral neuropathy**: Occurs frequently but the development of severe symptoms is rare. In severe cases, a dose reduction may be considered for all subsequent courses of PACLitaxel as per consultant guidance.
- **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. Dose reducing PACLitaxel may lessen the severity of arthralgias/myalgias; however, there is no data on efficacy of reduced doses in a curative setting. Dose reduction should be considered only if symptom severity precludes continuing PACLitaxel.
- **Hepatic Dysfunction**: Patients with hepatic impairment may be at increased risk of toxicity, particularly grade 3-4 myelosuppression.
- **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.

cycloPHOSphamide:

- **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.

DOXOrubicin:

- **Cardiac Toxicity**: DOXOrubicin is cardiotoxic and must be used with caution, if at all, in patients with severe hypertension or cardiac dysfunction.

DRUG INTERACTIONS:

- Avoid concurrent use with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). When necessary perform regular audiometric testing.
- Risk of drug interactions causing increased concentrations of PACLitaxel with CYP3A4 and CYP2C8 inhibitors.
- Risk of drug interactions causing decreased concentrations of PACLitaxel with CYP3A4 and CYP2C8 inducers.
- 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.

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- 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.

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Version	Date	Amendment	Approved By
1	26/09/2023		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.

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