Gemcitabine and CARBOplatin (AUC2) Therapy - 21 days

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of locally recurrent metastatic triple negative breast cancer	C50	00430a	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 gemcitabine are administered on day 1 and day 8 of a 21 day cycle until disease progression or unacceptable toxicity develops.

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

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate
1	1, 8	CARBOplatin	AUC 2	IV infusion	250ml glucose 5% over 30 mins
2	1, 8	Gemcitabine	1000mg/m^2	IV infusion	250ml NaCL 0.9% over 30mins

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 may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate 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, estimation using formulae may not give accurate results; 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 in the Cockcroft and Gault formula 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*.

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

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

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

S = 1.04 for females

ELIGIBILITY:

- Indication as above
- ECOG 0-1

EXCLUSIONS:

- Hypersensitivity to gemcitabine, CARBOplatin* or any of the excipients
- Pregnancy or Lactation

**If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation regimen, but only with immunology advice, premedication as advised, and a desensitisation regimen under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision)*

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Isotope GFR measurement (preferred) or GFR / Clearance estimation
- Audiometry and creatinine clearance as clinically indicated

Regular tests:

- Day 1: FBC, renal and liver profile
- Day 8: FBC

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
- Treatment will proceed on day 1 if the ANC ≥ 1 x 10^9/L and platelets ≥ 100 x 10^9/L
- If treatment on day 1 is delayed in order for these parameters to be reached then dose modifications should be made according to Table 1

Haematological:

Table 1: Dose modifications for gemcitabine and CARBOplatin for haematological toxicity on DAY 1 of cycle

ANC (x 10^9 /L)		Platelet count (x 10^9 /L)		Other haematological toxicity	Dose Gemcitabine	Dose Carboplatin
≥ 1	and	≥100			100 %	100%
First Episode					**Once resolved to ANC ≥ 1 and platelets ≥ 100**	
<1	**OR**	<100	**OR**	febrile neutropenia	Reduce dose to 80% of the original starting dose	Reduce dose to 80% of the original starting dose
Any	**and**	<25	**OR**	Bleeding associated with thrombocytopenia		
Second Episode					**Once resolved to ANC ≥ 1 and platelets ≥ 100**	
< 1	**OR**	<100	**OR**	febrile neutropenia	Reduce dose to 60% of the original starting dose	Reduce dose to 60% of the original starting dose.
Any	**And**	<25	**OR**	Bleeding associated with thrombocytopenia		

Table 2: Dose modifications for gemcitabine and CARBOplatin on day 8

ANC (x 10^9 /L)		Platelet count (x 10^9 /L)	Dose Gemcitabine	Dose CARBOplatin
≥1.0	and	≥100	100 %	100%
0.75-0.99	or	75-99	80% of Day 1 dose	80% of Day 1 dose
<0.75	or	<75	Omit dose*	Omit dose*
*Treatment omitted will not be re-instated within a cycle.				

Renal and Hepatic Impairment:

Table 3: Dose modification of gemcitabine and CARBOplatin in Renal Impairment

Drug	Renal Impairment	
	CrCl (ml/min)	**Dose**
Gemcitabine	≥30	100%
	<30	No need for dose adjustment is expected
	Haemodialysis	No need for dose adjustment is expected. Start haemodialysis 6-12 hrs after administration
CARBOplatin	See note below[a]	

[a]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of <60ml/min are at greater risk of developing myelosuppression
- If GFR between 20 to ≤ 30ml/min, CARBOplatin should be administered with extreme caution
- If GFR ≤ 20ml/min, CARBOplatin should not be administered at all
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration If isotope GFR is used, the dose can remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine increases, consideration should be given to remeasuring the GFR or to estimating it using Cockcroft & Gault or Wright formulae

Table 4: Dose modification of Gemcitabine and CARBOplatin in hepatic Impairment

Drug	Hepatic Impairment
Gemcitabine	Total bilirubin < 27 micromol/L: no dose adjustment is needed Total bilirubin ≥ 27 micromol/L: either start at 80% of the original dose and increase the dose if tolerated or start with full dose with active monitoring
CARBOplatin	No dose modification required

Table 5: Dose modification schedule based on adverse events

Adverse reactions	Recommended dose modification
Grade ≥ 2 Pneumonitis	**Discontinue gemcitabine**
Grade ≥ 3 Non-haematological toxicity (except nausea/vomiting) • First episode	Therapy with gemcitabine and carboplatin should be withheld (until toxicity has resolved to grade ≤ 1) and may be resumed with dose reduction of 20% from the initial dose of gemcitabine or carboplatin at discretion of prescribing consultant.
• Second episode	A second 20% dose reduction in either gemcitabine or carboplatin doses is allowed for recurrent Grade ≥ 3 Non-haematological toxicity.

• Third episode	**Discontinue treatment**

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL:

Gemcitabine: Low **(Refer to local policy)**

Carboplatin: Moderate **(Refer to local policy)**

PREMEDICATIONS: None usually required.

OTHER SUPPORTIVE CARE: No specific recommendations.

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.

Gemcitabine:

- **Renal Toxicity**: Irreversible renal failure associated with hemolytic uremic syndrome may occur (rare) with gemcitabine. Use caution with pre-existing renal dysfunction.
- **Pulmonary Toxicity**: Acute shortness of breath may occur with gemcitabine. Discontinue treatment with gemcitabine if drug-induced pneumonitis is suspected.
- **Cardiovascular:** Due to the risk of cardiac and/or vascular disorders with gemcitabine, particular caution must be exercised with patients presenting a history of cardiovascular events.
- **Infusion time:** Infusion time prolonged beyond 60 minutes has been shown to increase volume of distribution and has been associated with an increase in toxicity. However, given in the context of a fixed dose rate (FDR) regimen, prolonged infusions have also been reported to produce a higher response rate than standard regimens in association with a higher intracellular accumulation of its active metabolite (dFdCTP).

CARBOplatin:

- **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.
- **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.

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.
- CARBOplatin may interact with aluminium to form a black precipitate. Needles, syringes, catheters or IV administration sets that contain aluminium parts which may come into contact with CARBOplatin, should not be used for the preparation or administration of the drug.
- Current drug interaction databases should be consulted for more information.

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Version	Date	Amendment	Approved By
1	14/06/2017		Prof Maccon Keane
2	28/02/2018	Treatment table updated for standardization and clarified dose modifications for haematological toxicity	Prof Maccon Keane
3	16/01/2019	Standardization of dose modifications in hepatic impairment	Prof Maccon Keane
4	06/01/2021	Amended emetogenic potential	Prof Maccon Keane
5	22/09/2023	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing, renal impairment and creatinine value.Updated baseline tests and dose modifications sections.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.