Gemcitabine and Carboplatin (breast)

Indication

Second or third line chemotherapy for advanced breast cancer. Usually after previous chemotherapy with anthracyclines and taxanes.

ICD-10 codes

Codes pre-fixed with C50

Regimen details

Day	Drug	Dose	Route
1	Carboplatin	AUC 4*	IV infusion
1 and 8	Gemcitabine	1000 mg/m²	IV infusion

* Carboplatin dose calculated using the Calvert equation: **Carboplatin dose (mg) = AUC (CrCl +25)**
The creatinine clearance (CrCl) is calculated using the Cockcroft and Gault equation, however for patients where the creatinine level may not truly reflect renal function (e.g. in extremes of BSA or debilitated patients) an EDTA should be performed.
CrCl should be capped at 125mL/min.

Carboplatin dose may be increased to AUC 5 if well tolerated and no significant myelosuppression.

Cycle frequency

21 days

Number of cycles

Maximum 6 cycles

Administration

Day 1
Carboplatin is administered in 500mL glucose 5% over 30- 60 minutes.
Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Day 8
Gemcitabine administered in 250-500ml sodium chloride 0.9% over 30 minutes.

Patients should be observed closely for hypersensitivity reactions, particularly during the first and second infusions. Hypersensitivity reactions may occur within a few minutes following the initiation of the infusion of carboplatin. Facilities for the treatment of hypotension and bronchospasm **must** be available.
If hypersensitivity reactions occur, minor symptoms such as flushing or localised cutaneous reactions do not require discontinuation of therapy. The infusion may be temporarily interrupted and when symptoms improve restarted at a slower infusion rate. Chlorphenamine 10mg IV may be administered. Severe reactions, such as hypotension, bronchospasm or generalised rash/erythema require immediate discontinuation of carboplatin and appropriate therapy.

Pre-medication

If previous reaction to carboplatin: chlorphenamine 10mg IV and hydrocortisone 100mg IV may be given.

Emetogenicity

Day 1 has moderate-high emetic potential.
Day 8 has moderate-low emetic potential.

Additional supportive medication

Loperamide if required.
Antiemetics as per local guidelines
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy

Extravasation

Carboplatin – irritant (Group 3)
Gemcitabine – neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Calcium	14 days
Magnesium	14 days

Baseline EDTA if suspected or significant renal dysfunction.

Investigations - pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days

In addition FBC is required on day 8 prior to gemcitabine

Standard limits for administration to go ahead

If blood results not within range, authorisation to administer **must** be given by prescriber/ consultant

Investigation	**Limit**
Neutrophils	≥1.0 x 10^9/L
Platelets	≥100 x 10^9/L
Bilirubin	≤1.5 x ULN
Creatinine Clearance (CrCl)	> 30 mL/min

Dose modifications

- **Haematological toxicity**

Day	**Neutrophils** (x 10^9/L)		**Platelets** (x 10^9/L)	**Dose modification**	
				Carboplatin	**Gemcitabine**
Day 1	≥ 1.0	and	≥ 100	100%	100%
	< 1.0	or	< 99	Delay then 75%	Delay then 75%
Day 8	≥ 1.0	and	≥ 100	N/A	100%
	0.5 – 1.0	or	50-99	N/A	75%
	<0.5	or	< 50	N/A	Omit

If febrile neutropenia – reduce dose of carboplatin by 1 x AUC and gemcitabine to 75% for all future cycles.

- **Renal impairment**

If calculated CrCl falls by >10% from previous cycle, consider dose recalculation. If calculated CrCl improves the dose should not be increased unless there is a clear cause of renal function improvement (such as treatment of urinary tract obstruction).

CrCl (mL/min)	**Carboplatin dose**	**Gemcitabine dose**
> 30	100%	100%
20-30	EDTA then 100% dose	Consider dose reduction (consultant decision)
< 20	Omit	Consider dose reduction (consultant decision)

- **Hepatic impairment**

Bilirubin (x ULN)		**AST/ALT** (x ULN)	**Carboplatin dose**	**Gemcitabine dose**
≤ 1.5	and	≤ 1.5	100%	100%
1.5-3	or	1.5-3.5	100%	80%
> 3	or	> 3.5	Not recommended (consultant decision)*	

*transient increases in liver enzymes have been seen in patients being treated with both carboplatin and gemcitabine although no dose reduction is usually required.

- **Other toxicities**

Any Grade 3-4 toxicity (except mucositis and alopecia) – delay until ≤ Grade 1 toxicity and reduce dose. Discuss with consultant.

Gemcitabine should be discontinued at the first sign of microangiopathic haemolytic anaemia (such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevated bilbirubin, creatinine, blood urea nitrogen or LDH. Renal failure may not be reversible with discontinuation of therapy, dialysis may be required.

For **neurotoxicity**:

Grade	**Carboplatin dose**	**Gemcitabine dose**
0-1	100%	100%
2	50%	100%
3	Omit	100%
4	Discontinue	Discontinue

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Hypersensitivity reactions
Haemolytic uraemic anaemia
Pulmonary fibrosis
Electrolyte disturbances

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Diarrhoea, constipation
Peripheral neuropathy
Oedema

- **Other side effects**

Raised transaminases
Alopecia
Fatigue

Significant drug interactions – for full details consult product literature/ reference texts

Warfarin/coumarin anticoagulants: increased or fluctuating anticoagulant effects. Avoid if possible, consider switching patient to a low molecular weight heparin during treatment or if the patient continues taking an oral anticoagulant monitor the INR at least once a week and adjust dose accordingly.

Carboplatin only:
Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity
Clozapine: increased risk of agranulocytosis, avoid concomitant use
Diuretics: increased risk of nephrotoxicity and ototoxicity
Nephrotoxic drugs: increased nephrotoxicity ; not recommended
Phenytoin: carboplatin reduces absorption and efficacy of phenytoin

Additional comments

Nil

References

- Nagourney, RA et al; Clinical Breast Cancer 2008; 8 (5): 432 – 435
- Summary of Product Characteristics Carboplatin (Hospira) accessed on 22 Oct 2014 via www.medicines.org.uk
- Summary of Product Characteristics Gemcitabine (Lilly) accessed 22 Oct 2014 via www.medicines.org.uk

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