Gemcitabine and Carboplatin (gynae)

Indication

Palliative therapy for relapsed ovarian, fallopian tube or primary peritoneal cancer with late relapse (> 6 months) after previous treatment with a platinum or platinum and taxane.

Relapsed cervical cancer.

ICD-10 codes

Codes prefixed with C48, 53, 56, 57.

Regimen details

Day	Drug	Dose	Route
1	Carboplatin	AUC 4*	IV infusion
1 and 8	Gemcitabine	1000mg/m^2	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) a formal GFR measurement should be performed.
CrCl should be capped at 125mL/min.

Cycle frequency

21 days

Number of cycles

6 cycles

Administration

Carboplatin is administered in 250-500mL glucose 5% over 30-60 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.

Gemcitabine is administered in 250-500mL sodium chloride 0.9% over 30 minutes.

Pre-medication

Chlorphenamine 10mg IV and hydrocortisone 100mg IV may be given if there has been more than a 6 month gap between courses of treatment due to a possible reaction to carboplatin antibodies.

Emetogenicity

Day 1 has a moderate - high emetogenic potential
Day 8 has low emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.
Loperamide if required.
Proton pump inhibitor if required.
Consider ciprofloxacin 250-500mg BD days 5-14 (10 days total) following febrile neutropenia.

Extravasation

Carboplatin is an irritant (Group 3)
Gemcitabine is neutral (Group 1)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local policy)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
CA125	28 days

Baseline measured GFR if suspected or significant renal dysfunction.

Investigations – pre subsequent cycles

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

* In addition, FBC is required within 24 hours of 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
Creatinine Clearance (CrCl)	> 30mL/min (and <10% change in CrCl from previous cycle)
ALT/AST	< 1.5 x ULN
Bilirubin	< 1.5 xULN

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 reduce by 1 x AUC	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

In the case of febrile neutropenia, reduce dose of carboplatin by 1 x AUC and gemcitabine to 75% and consider prophylactic ciprofloxacin (see supportive medication).

- **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	Measured GFR then 100% dose	Consider dose reduction (consultant decision)
< 20	Discuss with consultant	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**

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 all other grade 3-4 toxicities (except alopecia) delay treatment until resolved to ≤ grade 1 and resume with 80% dose of carboplatin and gemcitabine. If further toxicity occurs consider additional dose reduction (discuss with consultant).

If delays of > 3 weeks or > 2 dose reductions, discontinue treatment.

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

- **Serious side effects**

Myelosuppression

Pulmonary fibrosis (rare)
Nephrotoxicity
Haemolytic uraemic syndrome

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Constipation, diarrhoea
Stomatitis and mucositis
Fatigue
Rash
Oedema
Ototoxicity
Electrolyte disturbances

- **Other side effects**

Mild alopecia
Elevated transaminases

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 or DOAC 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

In patients with significant frailty or co-morbidity where chemotherapy is nevertheless deemed appropriate, consider strategies to minimise toxicity such as reducing the carboplatin dose to AUC 3.

References

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- Summary of Product Characteristics Carboplatin (Hospira) accessed 12 August 2021via www.medicines.org.uk
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