

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) an EDTA 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 moderate – low emetogenic potential

Additional supportive medication

Mouthwashes as per local policy.

Loperamide if required.

H₂ antagonist or 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 EDTA 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

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	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
Creatinine Clearance (CrCl)	> 30mL/min (and <10% change in CrCl from previous cycle)

Dose modifications

• Haematological toxicity

Day	Neutrophils ($\times 10^9/L$)		Platelets ($\times 10^9/L$)	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

In the case of febrile neutropenia, reduce dose of carboplatin and gemcitabine to 80% 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	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**

Gemcitabine should be discontinued at the first sign of microangiopathic haemolytic anaemia (such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevated bilirubin, 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
 Infertility
 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: Avoid use due to elevations in INR. Switch to low molecular weight heparin during treatment.

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

- Pfisterer J, Plante M, Vergote I, du Bois A, Hirte H, Lacave AJ, et al. AGO-OVAR; NCIC CTG; EORTC GCG. Gemcitabine plus carboplatin compared with carboplatin in patients with platinum-sensitive recurrent ovarian cancer: an intergroup trial of the AGO-OVAR, the NCIC CTG, and the EORTC GCG. *J Clin Oncol* 2006 24(29):4699-707.
- Pfisterer J, Vergote I, Du Bois A, Eisenhauer, E. Combination therapy with gemcitabine and carboplatin in recurrent ovarian cancer. *Int J Gynecol Cancer*. 2005 May-Jun; 15 Suppl 1:36-41.
- Summary of Product Characteristics Carboplatin (Hospira) accessed 25 June 2014 via www.medicines.org.uk
- Summary of Product Characteristics Gemcitabine (Lilly) accessed 25 June 2014 via www.medicines.org.uk
- Allwood M, Stanley A, Wright P, editors. *The cytotoxics handbook*. 4th ed. Radcliffe Medical Press. 2002.

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