

## Gemcitabine and Carboplatin (Bladder)

### Indication

In patients unsuitable for treatment with cisplatin in the following indications:

- Palliative therapy for locally advanced or metastatic bladder or ureteric cancer
- Neo-adjuvant treatment of transitional cell carcinoma (consultant decision, better evidence for gemcitabine and cisplatin in this setting)

### ICD-10 codes

Codes prefixed with C67.

### Regimen details

Day	Drug	Dose	Route
1	Carboplatin	AUC 5*	IV infusion
1 and 8	Gemcitabine	1000mg/m <sup>2</sup>	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

Palliative: up to a maximum of 6 cycles

Neoadjuvant: Usually 3-4 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 carboplatin 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.

### 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

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 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	$\geq 1.0 \times 10^9/L$
Platelets	$\geq 100 \times 10^9/L$
Creatinine Clearance (CrCl)	$> 30\text{mL/min}$ (and $<10\%$ change in CrCl from previous cycle)
ALT/AST	$< 1.5 \times \text{ULN}$
Bilirubin	$< 1.5 \times \text{ULN}$

### Dose modifications

#### • Haematological toxicity

Day	Neutrophils ( $\times 10^9/L$ )		Platelets ( $\times 10^9/L$ )	Dose modification	
				Carboplatin	Gemcitabine
Day 1	$\geq 1.0$	and	$\geq 100$	100%	100%
	$< 1.0$	or	$< 100$	Delay then reduce by 1 x AUC	Delay then 75%
Day 8	$\geq 1.0$	and	$\geq 100$	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%.

- 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 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  
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.

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**References**

- Summary of Product Characteristics Carboplatin (Hospira) accessed 23 October 2023 via [www.medicines.org.uk](http://www.medicines.org.uk)
- Summary of Product Characteristics Gemcitabine (Hospira) accessed 23 October 2023 via [www.medicines.org.uk](http://www.medicines.org.uk)
- Allwood M, Stanley A, Wright P, editors. The cytotoxics handbook. 4<sup>th</sup> ed. Radcliffe Medical Press. 2002.
- Nogue-Aligneur, M. *et al.* Gemcitabine and Carboplatin in advanced transitional cell carcinoma of the urinary tract: an alternative therapy. *Cancer* 2003; 97(9):2180-6.
- Birtle, A. *et al.* Adjuvant chemotherapy in upper tract urothelial carcinoma (the POUT trial): a phase 3, open-label, randomised controlled trial. *Lancet* 2020; 395(10232):1268-1277

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