Gemcitabine and Carboplatin (NSCLC)

Indication

First-line chemotherapy for advanced (stage IIIB/IV) non-small cell lung cancer, where cisplatin is not appropriate.

(NICE CG121)

ICD-10 codes

Codes pre-fixed with C34

Regimen details

Day	Drug	Dose	Route
1 and 8	Gemcitabine	1250 mg/m²*	IV infusion
1	Carboplatin	AUC 6**	IV infusion

*Some protocols use 1000 mg/m^2 (Consultant decision)

** 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.

For patients with significant co-morbidities or WHO PS > 1 consider reducing doses of carboplatin and gemcitabine (Consultant decision)

Cycle frequency

21 days

Number of cycles

Maximum 4 cycles

Administration

Day 1

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

Following the gemcitabine, carboplatin is administered in 250-500mL glucose 5% over 30- 60 minutes

Days 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

Antiemetics as per local guidelines.
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

Consider prophylactic ciprofloxacin 250mg BD and fluconazole 50mg OD for 7 days, starting on day 7.
Loperamide if required.
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	< 100	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 (neutrophils < 0.5 x 10^9/L and fever with or without hospitalisation) – use 75% dose of carboplatin and gemcitabine 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**

Use gemcitabine in caution in hepatic impairment.
Raised transaminases do not seem to cause dose limiting toxicity. Transient increases in liver enzymes have been seen in patients being treated with both carboplatin and gemcitabine although no dose reduction is usually required.

If bilirubin > 1.5 x ULN, initiate gemcitabine at dose of 800 mg/m2.

- **Other toxicities**

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

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
Peripheral neuropathy
Hypersensitivity reactions
Haemolytic uraemic anaemia*
Pulmonary fibrosis
Electrolyte disturbances

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.

- **Frequently occurring side effects**

Nausea and vomiting
Mucositis, stomatitis
Diarrhoea, constipation
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

- National Institute of Health and Clinical Excellence Guideline CG121. Lung Cancer. The diagnosis and treatment of lung cancer Accessed via www.nice.org.uk (21 May 2014)
- Summary of Product Characteristics Carboplatin (Hospira) accessed via www.medicines.org.uk (21 May 2014)
- Summary of Product Characteristics GemzarR (Gemcitabine) (Lilly) accessed via www.medicines.org.uk (21 May 2014)
- A British Thoracic Oncology Group phase III trial of gemcitabine plus cisplatin at 80mg/m2 versus gemcitabine plus cisplatin at 50mg/m2 versus gemcitabine plus carboplatin AUC 6 in stage IIIB/IV non-small cell lung cancer (NSCLC). Version 4.4 06/02/07.

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Date: 13 November 2014