

Lung Pathway Group – Gemcitabine & Cisplatin in Non-Small Cell Lung Cancer (NSCLC)

Indication: First line treatment option in advanced or metastatic NSCLC

Regimen details:

Gemcitabine	1250 mg/m ²	IV	Days 1 and 8
Cisplatin	80 mg/m ²	IV	Day 1

Administration: Suggested hydration schedule:

Day 1

Furosemide 40mg orally

1 litre 0.9% Sodium Chloride + 20 mmol KCl + 1g MgSO₄ IV over 60 minutes

Gemcitabine in 250 – 500ml Sodium Chloride 0.9% IV over 30 min

Cisplatin in 1 litre Sodium Chloride 0.9% IV over 2 hours

1 litre Sodium Chloride 0.9% + 40 mmol KCl + 1g MgSO₄ IV over 2 hours

Then **either** 500ml Sodium Chloride 0.9% IV over 60 minutes **or** 500ml drinking water

Encourage oral hydration during treatment; for instance drink a glass of water every hour during treatment, and **at least a further 2 litres over the 24 hours following treatment.**

Weight should be recorded prior to and at the end of cisplatin treatment, and a strict fluid balance chart should be maintained. An average urine output of at least 100ml/hr must be maintained throughout treatment, and cisplatin infusion should not be commenced unless this urine output is achieved. For low urine output consider increasing the pre-hydration and diuretic regimen. Consider adding diuretics in weight-gain of 1.5 kg, or symptoms of fluid overload.

Aluminium containing equipment should not be used during preparation and administration of cisplatin.

Version: 1.0 Supersedes: all other versions	Approved by LCA Lung Pathway Chemotherapy Lead: Dr Rohit Lal	
Reason for Update: LCA Protocol Development	Approved by LCA Joint Delivery Subgroup Co-Chairs: Pauline McCalla & Rebecca Johl	
Prepared by: Lisa Yuen	Approved by LCA Medicines & Chemotherapy Steering Group Chair: Jamie Ferguson	
Second check by: Laura Cameron	Date prepared: November 2014	Review Date: November 2016
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Day 8 Gemcitabine in 250 – 500ml Sodium Chloride 0.9% IV over 30 min

Hypersensitivity reactions may occur, such as flushing, rash with or without pruritus, chest tightness, back pain, dyspnoea and fever or chills, usually during the first and second infusions and within a few minutes following the start of the infusion; the infusion should be slowed down or interrupted and the necessary supportive medication should be administered.

Severe reactions such as hypotension and/or bronchospasm or generalised rash/erythema requires immediate discontinuation. Availability of resuscitation equipment must be ensured as a standard precaution.

Frequency: Day 1 and 8, every 21 days for 4 to 6 cycles.

Pre-medication: Not routinely required

Anti- emetics: Day 1: High emetogenicity
Day 8: Low emetogenicity
Follow local anti-emetic policy

Supportive medication: Mouthcare as per local policy
Paracetamol / Chlorphenamine / Hydrocortisone can be given for administration-related reactions such as chills / fever.

Extravasation: Non-vesicant

Regular investigations: Prior to Cycle 1:

FBC	Day 1 (within 14 days)
LFTs	Day 1 (within 14 days)
U&Es	Day 1 (within 14 days)
CT scan	Baseline
EDTA	See comments
Audiogram	If clinically indicated

Comments:
GFR should be calculated using the Cockcroft & Gault formula; if the calculated GFR <60 or >120ml/min measure EDTA clearance before prescribing. Monitor trends in serum creatinine between treatments, if >25% from baseline value re-calculate GFR using the Cockcroft & Gault formula.

Prior to Day 8 (all cycles):
FBC

Day 8 (within 48 hours)

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Prior to Day 1 (all cycles):

FBC	Day 1 (within 72 hours)
LFTs	Day 1 (within 72 hours)
U&Es	Day 1 (within 72 hours)
Imaging	After 3 cycles

Toxicities: Myelosuppression, fatigue, alopecia (mild), mucositis, somnolence, proteinuria and haematuria, allergic skin rashes, flu-like syndrome, diarrhoea, oedema, asthenia, rarely pneumonitis, elevation of transaminases, neurotoxicity (ototoxicity), nephrotoxicity, nausea, vomiting, infertility/ ovarian failure

DOSE MODIFICATIONS

Haematological Toxicity

Prior to day 1

Neutrophils (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Dose
≥ 1.5	&	≥ 100	100% dose
< 1.5	&/or	< 100	Delay for 1 week. Repeat FBC, if recovered to above these levels, give 100% dose.

If neutrophils < 0.5 x 10⁹/L for more than 5 days or < 0.1 x 10⁹/L for more than 3 days, or platelets < 25 x 10⁹/L, or febrile neutropenia is diagnosed, or toxicity related delay is > 1 week gemcitabine dose should be reduced to 75% from previous dose (do not escalate for subsequent cycles).

Prior day 8

Neutrophils (x 10 ⁹ /L)		Platelets (x 10 ⁹ /L)	Gemcitabine Dose
> 1.0	&	> 100	Give 100% dose
0.5 – 0.9	or	75 - 99	Give 75% dose Dose can be re-escalated in subsequent cycles, providing the FBC has returned to normal limits.
< 0.5	or	< 75	Omit Re-assess on day 1 of the next cycle

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Non-haematological Toxicities**Renal Impairment**

Creatinine Clearance (ml/min)	Gemcitabine Dose
≥ 30	Give 100% dose
< 30	Use with caution, no specific dosing recommendations available

Creatinine Clearance (ml/min)	Cisplatin Dose
≥ 60	Give 100% dose
< 60	Contraindicated – consider carboplatin

Hepatic Impairment

Cisplatin No dose modifications required

Gemcitabine

Use gemcitabine with caution in the presence of hepatic dysfunction.

In clinical trials, gemcitabine was associated with transient elevations of serum transaminases in approximately 70% of patients. However, there is no evidence that longer duration of gemcitabine exposure or greater total cumulative gemcitabine dose increases hepatic toxicity. Administration of gemcitabine in patients with concurrent liver metastases or a pre-existing medical history of hepatitis, alcoholism, or liver cirrhosis may lead to exacerbation of the underlying hepatic insufficiency.

Bilirubin (µmol/L)		ALT or ALP	Gemcitabine Dose
> 27 and ≤ 30			Give 800mg/m ²
> 30	or	> 3 x ULN (or > 5 x ULN if liver metastases present)	Withhold and seek Consultant advice – high risk of sepsis

Dose modifications for other toxicities as appropriate**Neurotoxicity**

Neurotoxicity	Gemcitabine Dose	Cisplatin Dose
Grade 2	Give 100% dose	Give 50% dose or consider carboplatin
Grade 3 or 4	Discontinue	Discontinue

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Other toxicities

Grade	Stomatitis	Diarrhoea	Dose Reductions
1	Painless ulcers, erythema or mild soreness	Increase of 2-3 stools/day or mild increase in loose watery colostomy output	Give 100% doses
2	Painful erythema, edema, or ulcers but can eat	Increase of 4-6 stools, or nocturnal stools or mild increase in loose watery colostomy output	Omit until resolved, then resume at 100% doses For 2 nd occurrence, resume at 75% doses
3	Painful erythema, edema, or ulcers and cannot eat	Increase of 7-9 stools/day or incontinence, malabsorption, or severe increase in loose watery colostomy output	Omit until resolved, then resume at 75% doses
4	Mucosal necrosis, requires parenteral support	Increase of 10 or more stools/day or grossly bloody diarrhoea, or grossly bloody colostomy output or loose watery colostomy output requiring parenteral support, dehydration	Omit until resolved, then resume at 50% doses (except for mucositis – give 75% doses)

Doses reduced for toxicity should not be re-escalated

Location of regimen: Day case setting
delivery

Comments:

Electrolyte disturbances – Cisplatin

Disturbances in electrolytes can be a long term manifestation due to the cisplatin induced renal tubular dysfunction. Check electrolytes - additional supplementation of magnesium, calcium or potassium may be required

Haemolytic Uraemic Syndrome – Gemcitabine

Gemcitabine should be discontinued at the first signs of any evidence of micro-angiopathic haemolytic anaemia, such as rapidly falling haemoglobin with concomitant thrombocytopenia, elevation of serum bilirubin, serum creatinine, blood urea nitrogen, or LDH, which may indicate development of haemolytic uraemic syndrome. Renal failure may not be reversible, even with discontinuation of therapy, and dialysis may be required

Women of childbearing potential must use effective contraception during treatment.

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Sexually mature males are advised not to father a child during the treatment, and up to 6 months thereafter. If appropriate, male patients should be advised to seek counselling on sperm storage before starting treatment.

Drug interactions:

Gemcitabine is radiosensitiser
 Warfarin - increased risk of bleeding (Gemcitabine)
 Phenytoin, carbamazepine – Cisplatin decreases efficiency
 Nephrotoxic drugs (with Cisplatin)
 Aminoglycoside antibiotics-increased risk of ototoxicity with cisplatin

References:

Migliorino MR et al. Lung Cancer (2002) 35(3): 319-27
 Cardenal F et al. J Clin Oncol (1999) 17(1): 12-8
 Crino L et al. J Clin Oncol (1999) 17(11) 3522-30
 Rosell R et al. Semin oncol (1998) 25(4):27-34
 Gebbia V et al. Lung Cancer (2003) 39(2): 179-89
 Martoni A et al. Eur J Cancer (2005) 41(1): 81-92
 Ohe Y et al. Ann Oncol (2007) 18(2): 317-23)

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