

Lung Pathway Group – Pemetrexed and Cisplatin in Non-Small Cell Lung Cancer (NSCLC)

Indication:

NICE TA181

First line treatment option in advanced or metastatic **non-squamous** NSCLC (histology confirmed as adenocarcinoma or large cell carcinoma)

Performance status 0 - 1

Regimen details:

Pemetrexed	500 mg/m ²	IV	Day 1
Cisplatin	75 mg/m ²	IV	Day 1

Administration:

Suggested hydration schedule:

Furosemide 40mg orally

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

Pemetrexed in 100ml Sodium Chloride 0.9% over 10 minutes
30 minutes after pemetrexed:

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

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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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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.

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, every 21 days, for up to 6 cycles

Pre-medication: Oral dexamethasone 4mg BD for 3 days, starting the day prior to chemotherapy (to reduce incidence / severity of skin reactions as well as anti-emetic role).
In exceptional circumstances when dexamethasone pre-medication has been omitted the day before treatment, this can be replaced with dexamethasone 8mg IV administered one hour before treatment.

Anti- emetics: High emetogenicity
Follow Local Anti-emetic Policy

Supportive medication: Folic acid 400micrograms orally once a day starting at least 5 days before first treatment and continuing until 3 weeks after the last pemetrexed dose.
Vitamin B₁₂ (hydroxocobalamin) 1000micrograms by IM injection, start the week before first treatment, then once every 9 weeks (can be given on same day as pemetrexed) until 3 weeks after last pemetrexed dose.
Paracetamol / Chlorphenamine/Hydrocortisone can be given for administration-related reactions such as chills/fever.
Mouthcare as per local policy.

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Extravasation:	Non-vesicants	
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)
	Ca & Mg	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 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, skin rash, alopecia (mild), mucositis, diarrhoea, neurotoxicity (including ototoxicity), nephrotoxicity, ovarian failure/infertility, nausea/vomiting.

DOSE MODIFICATIONS

Haematological Toxicity

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. For >1 delay, a 25% dose reduction of both cisplatin and pemetrexed may be considered – discuss with the Consultant.

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Non-haematological Toxicities

Renal Impairment

Creatinine Clearance (ml/min)	Pemetrexed Dose
≥ 45	Give 100% dose
< 45	Not recommended – discuss with consultant

Creatinine Clearance (ml/min)	Cisplatin Dose
≥ 60	Give 100% dose
< 60	Contra-indicated - consider carboplatin

Hepatic Impairment

Cisplatin No dose modifications required

Bilirubin	ALP, ALT, AST	Pemetrexed Dose
≤1.5 x ULN	≤3 x ULN	100% dose
	≤5 x ULN if liver involvement	

No information is available on dose reduction for pemetrexed in more severe hepatic impairment - discuss with consultant

Dose modifications for other toxicities as appropriate

Neurotoxicity

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

Other toxicities

	Pemetrexed Dose	Cisplatin Dose
Any grade 2 toxicity	Give 100% dose	Give 100% dose
Any grade 3 or 4 toxicities (except mucositis)	Give 75% of previous dose	Give 75% of previous dose
Diarrhoea (any grade) requiring hospitalisation	Give 75% of previous dose	Give 75% of previous dose
Grade 3 or 4 mucositis	Give 50% of previous dose	Give 100% of previous dose Grade 4 mucositis give 75% of previous dose

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If patient suffers any Grade 3 or 4 toxicity after 2 dose reductions, treatment must be reviewed by Consultant

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
Women of childbearing potential must use effective contraception during treatment.
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: Phenytoin, Carbamazepine
Nephrotoxic drugs, Ototoxic drugs
Non-steroidal anti-inflammatory drugs should be avoided from 5 days before each dose of pemetrexed until 2 days after each dose.
Live vaccines
Concomitant yellow fever vaccine is contra-indicated
Increased monitoring of INR levels is required with anticoagulants

References: Scagliotti et al. (2008): JCO, Vol 26(21)

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