Cisplatin and Pemetrexed (NSCLC, mesothelioma)

Indication

First-line treatment of locally advanced or metastatic non-small cell lung cancer (NSCLC) if the histology of the tumour has been confirmed as adenocarcinoma or large cell carcinoma.
(NICE TA181)

Malignant pleural mesothelioma only in patients with WHO PS 0 or 1 or who have advanced disease and surgical resection is considered inappropriate.
(NICE TA135)

ICD-10 codes

Codes pre-fixed with C34, C45.

Regimen details

Day	Drug	Dose	Route
1	Pemetrexed	500 mg/m^2	IV infusion
1	Cisplatin	75mg/m^2	IV infusion

Cycle frequency

21 days

Number of cycles

4 cycles (NSCLC) or 6 cycles (mesothelioma). For patients with NSCLC consider maintenance pemetrexed after 4 cycles (CDF funding required)

Administration

Pemetrexed is administered first in 100mL sodium chloride 0.9% over 10 minutes.

Cisplatin is administered in 500mL sodium chloride 0.9% over 60 minutes following the pre and post hydration protocol below.

Infusion Fluid & Additives	Volume	Infusion Time
Sodium Chloride 0.9%	1000mL	60 minutes
Mannitol 20% **OR** Mannitol 10%	200mL 400mL	10 minutes 15 minutes
Ensure urine output > 100mL / hour prior to giving cisplatin. Give a single dose of furosemide 20mg iv if necessary.		
Cisplatin	500mL	60 minutes
Sodium Chloride 0.9% + 2g $MgSO_4$ + 20mmol KCl	1000mL	2 hours
TOTAL	**2700 or 2900mL**	**4 hours 10 minutes or 4 hours 15 minutes**

Note: Patients with magnesium or potassium below the normal range should have 2g $MgSO_4$ and 20mmol KCl added to the pre-hydration bag and the duration of the infusion increased to 2 hours.

Patients should be advised to drink at least 2 litres of fluid over the 24 hours following cisplatin.

Pre-medication

Vitamin B12 (hydroxycobalamin) 1mg IM in the week preceding the first cycle and then approximately every 9 weeks (i.e. every 3 cycles) until pemetrexed treatment is completed. Pemetrexed should be administered no earlier than 48 hours after vitamin B12 injection for the first dose. Subsequent vitamin B12 injections may be administered on the same day as pemetrexed.
Folic acid 400 microgram PO OD should be started at least 1 week before first cycle (with a minimum of 5 doses taken in the 7 days preceding the first dose) and continued until 3 weeks after last cycle.
Dexamethasone 4mg PO BD for 3 days should be started 24 hours before chemotherapy.
Antiemetics as per local guidelines.

Emetogenicity

This regimen has severe emetic potential.

Additional supportive medication

Loperamide if required.
H_2 antagonist or proton pump inhibitor if required.
Mouthwashes as per local policy.
If magnesium levels < normal reference range refer to local magnesium replacement guidelines.

Extravasation

Cisplatin is an exfoliant (Group 4)
Pemetrexed is an inflammatant (Group 2)

Investigations – pre first cycle

Investigation	**Validity period** (or as per local practice)
FBC	14 days
U+E (including creatinine)	14 days
LFTs	14 days
Magnesium	14 days
Calcium	14 days

Consider formal EDTA measurement of creatinine clearance in patients with a low body surface area.

Investigations – pre subsequent cycles

Investigation	**Validity period** (or as per local practice)
FBC	96 hours
U+E (including creatinine)	7 days
LFTs	7 days
Magnesium	7 days
Calcium	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	≥1.5 x 10^9/L
Platelets	≥100 x 10^9/L
Creatinine Clearance (CrCl)	> 60 mL/min
Bilirubin	<1.5 x ULN
ALT/AST	<3 x ULN or < 5 x ULN in presence of liver metastases
Alkaline phosphatase	<3 x ULN or < 5 x ULN in presence of liver metastases

Dose modifications

For non-haematological toxicity delay treatment until resolved to ≤ grade 1.

- **Haematological toxicity**

If neutrophils < 1.5 x 10^9/L and platelets < 100 x 10^9/L delay for 1 week. If resolved then continue with 100% dose. If 2 or more delays then reduce doses of cisplatin and pemetrexed to 75%.

Where possible subsequent cycles should be modified according to nadir FBC:
Nadir neutrophils < 0.5 x 10^9/L and platelets ≥ 50 x 10^9/L – reduce cisplatin and pemetrexed to 75% of previous dose.
Nadir platelets <50 x 10^9/L (regardless of neutrophils) – reduce cisplatin and pemetrexed to 50% of previous dose.

- **Renal impairment**

CrCl (mL/min)	**Cisplatin dose**
≥ 60	100%
50-59	75%
40-49	50% (consider switching to carboplatin AUC 5)
< 40	Contraindicated

Pemetrexed should NOT be administered if CrCl <45 mL/min.

- **Hepatic impairment**

Pemetrexed:
No information available for patients with bilirubin > 1.5 x ULN and/or AST/ALT > 3 x ULN (5 x ULN if liver metastases present) – consultant decision.

Cisplatin:
No dose modification required.

- **Other toxicities**

Mucositis
Grade 3-4: reduce pemetrexed to 50% dose and continue with 100% dose cisplatin.

Neurotoxicity
Grade 2: reduce cisplatin to 50% dose and continue with 100% dose pemetrexed.
Grade 3-4: discontinue cisplatin

Any other grade 3-4 toxicity: reduce cisplatin and pemetrexed to 75% of previous dose.

Adverse effects - for full details consult product literature/ reference texts

- **Serious side effects**

Myelosuppression
Infertility
Ototoxicity
Nephrotoxicity
Peripheral neuropathy

- **Frequently occurring side effects**

Myelosuppression
Nausea and vomiting
Mucositis, stomatitis
Diarrhoea

Oedema
Haematuria

- **Other side effects**

Alopecia
Rash
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.

Aminoglycoside antibiotics: increased risk of nephrotoxicity and ototoxicity when given within 2 weeks of cisplatin.

Diuretics: increased risk of nephrotoxicity and ototoxicity

Nephrotoxic drugs: increased nephrotoxicity ; not recommended

Ototoxic drugs: increased risk of ototoxicity

Phenytoin: cisplatin reduces absorption and efficacy of phenytoin, monitor levels and adjust dose as necessary.

Anti-gout agents: cisplatin may increase plasma concentration of uric acid therefore dose adjustments may be required to control hyperuricaemia and gout.

Non-steroidal anti-inflammatory drugs (NSAIDs) should be avoided from 5 days before each dose of pemetrexed until 2 days after each dose.

Additional comments

References

- National Institute of Health and Clinical Excellence Guideline TA181. Accessed via www.nice.org.uk (04 June 2014)
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- Scagliotti GV, Parikh P, von Pawel J, Biesma B, Vansteenkiste J, Manegold C, et al. Phase III Study Comparing Cisplatin Plus Gemcitabine With Cisplatin Plus Pemetrexed in Chemotherapy-Naïve Patients With Advanced-Stage Non-Small-Cell Lung Cancer. J Clin Oncol 2008 26 (21): 3543-3551.
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