PEMEtrexed and CISplatin Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.	C45	00317a	Hospital
First line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).	C34	00317b	Hospital

TREATMENT:

The starting dose of the drugs detailed below may be adjusted downward by the prescribing clinician, using their independent medical judgement, to consider each patients individual clinical circumstances.

PEMEtrexed and CISplatin are administered once every 21 days for a maximum of 4-6 cycles until disease progression or unacceptable toxicity develops.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	PEMEtrexed	500mg/m^2	IV infusion	100ml 0.9% NaCl over 10min	Every 21 days
2	1	[a]CISplatin	75mg/ m^2	IV infusion	1000ml 0.9% NaCl over 2 hours to start 30 min after completion of PEMEtrexed	Every 21 days
		Folic Acid or multivitamin containing 350-1000 micrograms folic acid	350-1000 micrograms[b]	PO		

[a]**Pre and post hydration therapy required for CISplatin**

See local hospital policy recommendations.

Suggested prehydration for CISplatin therapy:

- Administer 1000ml NaCl 0.9% over 1 hour.
- Administer CISplatin as described above

Post hydration:

- Administer 1000ml NaCl 0.9% with 10mmol magnesium sulphate ($MgSO_4$) and 20mmol potassium chloride (KCl) over 2 hours

Mannitol 10% may be used to as per local policy to induce diuresis, although there is no conclusive evidence that this is required. The routine use of furosemide to increase urine flow is not recommended unless there is evidence of fluid overload (4, 5).

[b] At least five doses of folic acid must be taken during the seven days preceding the first dose of PEMEtrexed, and dosing must continue during the full course of therapy and for 21 days after the last dose of PEMEtrexed.

See Premedications for further treatment required.

PEMEtrexed is physically incompatible with diluents containing calcium, including lactated Ringer's injection and Ringer's injection.

ELIGIBILITY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to PEMEtrexed, CISplatin or any of the excipients
- Pregnancy and Lactation
- Creatinine clearance < 45ml/min
- Pre-existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus

PRESCRIPTIVE AUTHORITY:

The treatment plan must be initiated by a Consultant Medical Oncologist.

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Audiology and creatinine clearance if clinically indicated

Regular tests:

- FBC, renal and liver profile prior to each cycle

Disease monitoring:

Disease monitoring should be in line with the patient's treatment plan and any other test/s as directed by the supervising Consultant.

DOSE MODIFICATIONS:

- Any dose modification should be discussed with a Consultant.

Haematological:

- Dose adjustments at the start of a cycle should be based on nadir haematologic counts or maximum non-haematologic toxicity from the preceding cycle of therapy.
- Treatment may be delayed to allow sufficient time for recovery.
- Upon recovery patient should be retreated using the guidelines below.

Table 1: Dose modifications for haematological toxicity of PEMEtrexed and CISplatin

Based on Day 1 counts			
ANC (x10^9/L)		**Platelets (x 10^9/L)**	**Dose of PEMEtrexed and CISplatin**
≥ 1.5	and	≥ 100	100%
< 1.5	or	<100	Delay
Based on nadir counts			
≥ 0.5	and	≥ 50	100%
<0.5	and	≥ 50	75% of previous dose
any	and	<50	75% of previous dose
any	and	<50 with bleeding[a]	50% of previous dose

[a] CTC v2.0; NCI 1998 definition of ≥CTC Grade 2 bleeding

Renal and Hepatic Impairment:

Table 2: Dose modification of CISplatin and PEMEtrexed in renal and hepatic impairment

	Renal Impairment		Hepatic Impairment			
CISplatin	**CrCl (ml/min)**	**Dose**	No dose reduction necessary			
	≥60	100%				
	45-59	75%				
	<45	Consider CARBOplatin				
PEMEtrexed	**CrCl(ml/min)**	**Dose**	**Bilirubin**		**Aminotransferases**	
	≥45	100%	>1.5 x ULN	and/or or	> 3 x ULN (hepatic metastases absent) > 5 x ULN (presence of hepatic metastases	Not recommended. **Clinical decision**
	<45	Not recommended				

Management of adverse events:

Table 3: Dose Modification of PEMEtrexed and CISplatin for Adverse Events

Adverse reactions	Recommended dose modification
Non-haematologic toxicities [a,b]	
Any grade ≥3 toxicity other than mucositis or Any diarrhoea requiring hospitalisation (irrespective of grade) or grade ≥3 diarrhoea	Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at 75% of previous dose for both PEMEtrexed and CISplatin
Grade ≥3 mucositis	Withhold treatment until resolution to less than or equal to patient's pre-therapy value Resume at 50% of previous dose for PEMEtrexed and at 100% of previous dose for CISplatin
Grade ≥3 toxicity after 2 dose reductions	Discontinue
Neurotoxicity	
Grade 2	Reduce dose of CISplatin to 50% of previous dose
Grade 3-4	Discontinue CISplatin and PEMEtrexed
Haematologic Toxicity	
Grade ≥3 toxicity after 2 dose reductions	Discontinue

[a] CTC v2.0; NCI 1998; [b] Excluding neurotoxicity

SUPPORTIVE CARE:

EMETOGENIC POTENTIAL: High (**Refer to local policy).**

PREMEDICATIONS:

- A corticosteroid should be given the day prior to, on the day of, and the day after PEMEtrexed administration. The corticosteroid should be equivalent to 4 mg of dexamethasone administered orally twice a day.
- Intramuscular injection of vitamin B_{12} (hydroxycobolamin) (1,000 micrograms) in the week preceding the first dose of PEMEtrexed and once every three cycles thereafter. Subsequent vitamin B_{12} injections may be given on the same day as PEMEtrexed.

OTHER SUPPORTIVE CARE:
None usually required.

ADVERSE EFFECTS / REGIMEN SPECIFIC COMPLICATIONS

The adverse effects listed are not exhaustive. Please refer to the relevant Summary of Product Characteristics for full details.

- **Myelosuppression:** Usually the dose limiting toxicity with PEMEtrexed. PEMEtrexed should not be given to patients until absolute neutrophil count (ANC) returns to $1.5x10^9$/L and platelet count returns to $100x10^9$ /L. Dose reductions for subsequent cycles are based on nadir ANC, platelet count and maximum non-haematologic toxicity seen from the previous cycle.
- **Skin reactions:** Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions.
- **Cardiotoxicity:** Serious cardiovascular events including MI and cerebrovascular events have been uncommonly reported usually when PEMEtrexed is given in combination with another cytotoxic agent. Most of the patients in whom these events have been observed had pre-existing cardiovascular risk factors.
- **Renal Toxicity:** Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics.
    - Serious renal events, including acute renal failure, have been reported with PEMEtrexed alone or in association with other chemotherapeutic agents.
    - Nephrogenic diabetes insipidus and renal tubular necrosis were also reported in post marketing setting with PEMEtrexed alone or with other chemotherapeutic agents. Most of these events resolved after PEMEtrexed withdrawal. Patients should be regularly monitored for acute tubular necrosis, decreased renal function and signs and symptoms of nephrogenic diabetes insipidus (e.g. hypernatraemia).
- Ototoxicity and sensory neural damage should be assessed by history prior to each cycle.

DRUG INTERACTIONS:

- In patients with normal renal function (CrCl > 80 ml/min), high doses of non-steroidal anti-inflammatory drugs (NSAIDs, such as ibuprofen > 1600 mg/day) and aspirin at higher dose (> 1.3 g daily) may decrease PEMEtrexed elimination and, consequently, increase the occurrence of PEMEtrexed adverse events.
- The concomitant administration of PEMEtrexed with NSAIDs or aspirin at higher dose should be avoided for 2 days before, on the day of, and 2 days following PEMEtrexed administration on patients with mild to moderate renal insufficiency (CrCl from 45 to 79 ml/min).
- In patients with mild to moderate renal insufficiency eligible for PEMEtrexed therapy, NSAIDs with long elimination half-lives should be interrupted for at least 5 days prior to, on the day of, and at least 2 days following PEMEtrexed administration.
- Nephrotoxic drugs (e.g. loop diuretics and aminoglycosides) may decrease the clearance of PEMEtrexed.
- Concomitant administration of substances that are also tubularly secreted (e.g. probenecid, penicillin) could potentially result in delayed clearance of PEMEtrexed.
- Avoid concurrent use of CISplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Current drug interaction databases should be consulted for more information.

REFERENCES:

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Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	02/05/2018	Updated with new Regimen Template, updated exclusions, CISplatin hydration recommendations, dosing in renal impairment and adverse reactions	Prof Maccon Keane
3	29/04/2020	Reviewed. Update of adverse events.	Prof Maccon Keane
4	23/9/2020	Clarification of number of cycles	Prof Maccon Keane
5	24/06/2021	Updated CISplatin hydration protocol	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.