PEMEtrexed and CARBOplatin Therapy

INDICATIONS FOR USE:

INDICATION	ICD10	Regimen Code	Reimbursement Status
Treatment of chemotherapy naïve patients with unresectable malignant pleural mesothelioma.	C45	00318a	Hospital
First line treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC).	C34	00318b	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 CARBOplatin are administered once every 21 days for 4-6 cycles followed by maintenance PEMEtrexed monotherapy (Reference NCCP regimen 00222) or until disease progression or unacceptable toxicity develops.

Facilities to treat anaphylaxis MUST be present when systemic anti-cancer therapy (SACT) is administered.

Admin. Order	Day	Drug	Dose	Route	Diluent & Rate	Cycle
1	1	PEMEtrexed	500mg/m^2	IV infusion	100ml 0.9% NaCl over 10mins	Every 21 days
2	1	CARBOplatin	AUC 5	IV infusion	500ml glucose 5% over 30 mins	Every 21 days
		Folic Acid or multivitamin containing 350-1000 micrograms folic acid	350-1000micrograms[a]	PO		
[a] 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.						

CARBOplatin dose:

The dose in mg of CARBOplatin to be administered is calculated as follows:

Dose (mg) = target AUC (mg/ml x min) x (GFR ml/min +25)

- **Measured GFR** (e.g. nuclear renogram) is preferred whenever feasible.
- Estimation of GFR may be performed using the Wright formula to estimate GFR or the Cockcroft and Gault formula to estimate creatinine clearance.
- The GFR used to calculate the AUC dosing should not exceed 125ml/min.

• For obese patients and those with a low serum creatinine, for example, due to low body weight or post-operative asthenia, estimation using formulae may not give accurate results; measured GFR is recommended.

- where obesity (body mass index [BMI] ≥ 30 kg/m^2) or overweight (BMI 25-29.9) is likely to lead to an overestimate of GFR and isotope GFR is not available the use of the adjusted ideal body weight in the Cockcroft and Gault formula may be considered.
- where serum creatinine is less than 63 micromol/L, the use of a creatinine value of 62 micromol/L or a steady pre-operative creatinine value may be considered.

• These comments do not substitute for the clinical judgement of a physician experienced in prescription of CARBOplatin.

WRIGHT FORMULA

There are two versions of the formula depending on how serum creatinine values are obtained, by the kinetic Jaffe method or the enzymatic method. The formula can be further adapted if covariant creatine kinase (CK) values are available (not shown).

1. *SCr measured using enzymatic assay.*

$$\text{GFR (ml/min)} = \frac{(6230 - 32.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.23 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

2. *SCr measured using Jaffe assay*

$$\text{GFR (ml/min)} = \frac{(6580 - 38.8 \times \text{Age}) \times \text{BSA} \times (1 - 0.168 \times \text{Sex})}{\text{SCr (micromol/min)}}$$

Key: Sex = 1 if female, 0 if male; Age in years; BSA= DuBois BSA

COCKCROFT-GAULT FORMULA

$$\text{GFR (ml/min)} = \frac{S \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{serumcreatinine (micromol/L)}}$$

S= 1.04 for females and 1.23 for males

ELIGIBILTY:

- Indications as above
- ECOG 0-2

EXCLUSIONS:

- Hypersensitivity to PEMEtrexed, CARBOplatin* or any of the excipients
- Pregnancy and Lactation
- Pre existing neuropathies ≥ grade 2
- Significant hearing impairment/tinnitus

*If it is felt that the patient may have a major clinical benefit from CARBOplatin, it may in exceptional circumstances be feasible to rechallenge a patient with a prior mild hypersensitivity reaction e.g. using a desensitisation protocol, but only with immunology advice, premedication as advised, and a desensitisation protocol under carefully controlled conditions with resuscitation facilities available and medical and/or ITU/ HDU supervision

PRESCRIPTIVE AUTHORITY:

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

TESTS:

Baseline tests:

- FBC, renal and liver profile
- Isotope GFR measurement (preferred) or GFR / Clearance estimation
- 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 CARBOplatin

Based on Day 1 counts			
ANC (x10^9/L)		**Platelets (x 10^9/L)**	**Dose of PEMEtrexed and CARBOplatin**
<1	and/or	<75	Delay treatment for one week
Doses for subsequent cycles are reduced by 25% if ANC is 1-1.49 x10^9/L or platelets are 75 to 99 x10^9/L on day 22 after preceding cycle			
Based on nadir counts			
≥ 0.5	and	≥ 50	100%
<0.5	and	≥ 50	75% of previous dose
any	and	<50	50% of previous dose
Consider discontinuing therapy if a patient qualifies for a third dose reduction or a cycle is delayed by more than 21 days.			
Dose reductions should be maintained for subsequent cycles			

Renal and Hepatic Impairment:

Table 2: Dose modification of CARBOplatin and PEMEtrexedin renal and hepatic impairment

	Renal Impairment		**Hepatic Impairment**			
CARBOplatin	See note below[b]		No dose reduction necessary			
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				

[b]Renal dysfunction and CARBOplatin:

- Patients with creatinine clearance values of < 60ml/min are at greater risk to develop myelosuppression.
- In case of GFR ≤ 20ml/min CARBOplatin should not be administered at all.
- If Cockcroft & Gault or Wright formula are used, the dose should be calculated as required per cycle based on a serum creatinine obtained within 48 hrs of drug administration.
- If isotope GFR is used, the dose should remain the same provided the serum creatinine is ≤110% of its value at the time of the isotope measurement. If the serum creatinine is higher than this, consideration should be given to remeasuring the GFR or to recalculating using Cockcroft & Gault or Wright formulae.

Management of adverse events:

Table 3: Dose Modification of PEMEtrexed and CARBOplatin 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 CARBOplatin
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 CARBOplatin
Grade ≥3 toxicity after 2 dose reductions	Discontinue
Neurotoxicity	
Grade 2	Reduce dose of CARBOplatin to 50% of previous dose
Grade 3-4	Discontinue CARBOplatin 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

PEMEtrexed : Low (Refer to local policy).

CARBOplatin : 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.

PEMEtrexed

- **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:** 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).

CARBOplatin

- **Hypersensitivity:** Reactions to CARBOplatin may develop in patients who have been previously exposed to platinum therapy. However allergic reactions have been observed upon initial exposure to CARBOplatin.
- **Neurotoxicity and ototoxicity:** 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 CARBOplatin with nephrotoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS) due to additive nephrotoxicity. If necessary monitor renal function closely.
- Avoid concurrent use of CARBOplatin with ototoxic drugs (e.g. aminoglycosides, furosemide, NSAIDS). When necessary perform regular audiometric testing
- Current drug interaction databases should be consulted for more information.

REFERENCES:

1. Ceresoli GL. Zucali PA et al. Phase II study of pemtrexed plus carboplatin in Malignantpleual mesothelioma. J ClinOncol 2006;24 (9);1443-1447
2. Gronberg BH, Bremnes RM et al.Phase III study by the Norwegian lung cancer study group: pemetrexed plus carboplatin compared with gemcitabine plus carboplatin as first-line chemotherapy in advanced non-small-cell lung cancer. J ClinOncol. 2009; 27:3217.
3. Ekhart C, Rodenhuis S et al. Carboplatin dosing in overweight and obese patients with normal renal function, does weight matter? Cancer ChemotherPharmacol 2009;64:115-122.
4. Appropriate chemotherapy dosing for obese adult patients with cancer:American Society of Clinical Oncology Clinical Practice Guideline. J ClinOncol 2012; 30 (13) 1553-1561

5. Krens S D, Lassche,Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. Lancet Onco/2019; 20:e201-08. https://doi.org/10.1016/S1470-2045(19)30145-7
6. NCCP Classification Document for Systemic Anti-Cancer Therapy (SACT) Induced Nausea and Vomiting. V5 2023. Available at: https://www.hse.ie/eng/services/list/5/cancer/profinfo/chemoprotocols/nccp-classification-document-for-systemic-anti-cancer-therapy-sact-induced-nausea-and-vomiting.pdf
7. PEMEtrexed (ALIMTA®) Summary of Product Characteristics.Accessed July 2023 . Available at: https://www.ema.europa.eu/en/documents/product-information/alimta-epar-product-information_en.pdf
8. Carboplatin Summary of Product Characteristics. Accessed July 2023. Available at: https://www.hpra.ie/img/uploaded/swedocuments/LicenseSPC_PA0585-024-001_12082008145934.pdf

Version	Date	Amendment	Approved By
1			Prof Maccon Keane
2	02/05/2018	Applied new NCCP regimen template,updated dosing in hepatic impairment, adverse reactions and drug interactions	Prof Maccon Keane
3	29/04/2020	Reviewed. Update of exclusions and adverse events.	Prof Maccon Keane
4	29/09/2023	Updated CARBOplatin infusion time. Updated standard wording for CARBOplatin dosing, renal dysfunction and creatinine value. Updated baseline tests and exclusions section.	Prof Maccon Keane

Comments and feedback welcome at oncologydrugs@cancercontrol.ie.