Systemic Anti Cancer Treatment Protocol

Cisplatin with Pemetrexed
Mesothelioma

PROTOCOL REF: MPHACICAME
(Version No: 1.2)

Approved for use in:

Mesothelioma patients with PS0 or 1

Dosage:

Drug	Dose	Route	Frequency
Pemetrexed	500mg/m^2	IV Infusion	Every 21 days
Cisplatin	75mg/m^2	IV Infusion	Every 21 days

Repeat every 21 days for 4 to 6 cycles

Supportive Treatments:

Vitamin B12 intra muscular injection should be administered in the week preceding the 1st cycle. Vitamin B12 should be given every 9 weeks thereafter (every 3rd treatment cycle) on the same day as treatment.

Folic acid 400 micrograms once daily during treatment starting least five days before the first dose of pemetrexed, and continuing until 21 days after the last dose of pemetrexed.

Anti-emetic risk - High

Aprepitant 125mg to be taken on day 1, an hour before chemotherapy and 80mg to be taken as a single dose on day 2 and day 3.

Dexamethasone 4mg twice daily for 5 days, staring day before pemetrexed. If dexamethasone premedication has not been commenced then administer 8mg intravenously 30 minutes prior to pemetrexed, and then continue with the remainder of the oral doses.

Domperidone 10mg tablets, to be taken up to three times a day as required

Extravasation risk:

Pemetrexed: Neutral

Cisplatin: Exofoliant

Carboplatin: Irritant

Refer to the network guidance for the prevention and management of extravasation

Interactions

Aminoglycosides e.g. gentamicin, vancomycin and diuretics

Increased risk of nephrotoxicity and ototoxicity. Renal function should be well monitored and audiometric tests carried out as indicated.

Non-steroidal anti-inflammatory drugs:

These should be avoided from 5 days before each dose of pemetrexed until 2 days after each dose. If concomitant administration of NSAIDs is necessary, patients should be monitored closely for toxicity, especially myelosuppression, renal impairment and gastrointestinal toxicity.

Please consult summary of product characteristics via https://www.medicines.org.uk/emc for full list of interactions.

Administration:

- **Review patient's fluid intake over the previous 24 hours**
- **Review common toxicity criteria and performance status**
- **Calculate creatinine clearance using Cockcroft and Gault equation:**

Male patients $\frac{1.23 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L)}}$

Female patients $\frac{1.04 \times (140 - \text{age}) \times \text{weight (kg)}}{\text{Serum Creatinine (micromol/L}}$

Day	Drug	Dose	Route	Diluent and rate
1	**Aprepitant** 1 hour before chemotherapy	**125mg**	PO	(80mg to be taken as a single dose on day 2 and day 3)
	Ondansetron	**24mg**	PO	30mins before chemotherapy
	Furosemide	**20mg**	PO	
	Pemetrexed	**500mg/m^2**	IV	In 100mL sodium chloride 0.9% over 10 minutes
	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)	IV over 90 minutes		
	Cisplatin	**75mg/m^2**	IV	In 1000mL Sodium Chloride 0.9% over 90 minutes
	Sodium Chloride 0.9% 1000mL (+ 20mmol Potassium Chloride)	IV over 90 minutes		

If cisplatin cannot be administered due to tinnitus or renal impairment (creatinine clearance <45ml/min) then carboplatin may be considered as an alternative:

Day	Drug	Dose	Route	Diluent and rate
1	**Ondansetron** 30mins before chemotherapy	**16mg**	PO	
	Pemetrexed*	**500mg/m^2**	IV	In 100mL sodium chloride 0.9% over 10 minutes
	Carboplatin	**AUC 5**	IV	In 500mL glucose 5% over 60 minutes

***Please note that it is a clinical decision if pemetrexed should be given in patients with a creatinine clearance of less than 45ml/min. Pemetrexed may be hazardous in severe renal impairment.**

Main Toxicities:

Haematological: Myelosuppression: neutropenia, thrombocytopenia, anaemia

Gastrointestinal: Anorexia, nausea, vomiting and diarrhoea, mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), bitter or metallic taste disturbance,

Alopecia, fatigue, loss of fertility.

Cisplatin	
Nephrotoxicity	Urine output of 100 mL/hour or greater will help minimise cisplatin nephrotoxicity
Neuropathies	May be irreversible and may manifest by paresthesia, loss of muscle reflex and a sensation of vibrations. A neurologic examination must be carried out at regular intervals.
Ototoxicity	Observed in up to 31% of patients can be unilateral or bilateral and tends to become more frequent and severe with repeated doses; consider audiometry and referral to ENT specialist
Additional side effects	Anaphylactic-like reactions
Pemetrexed	
Skin reactions	Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions
Radiation pneumonitis **Radiation recall**	In patients treated with radiation either prior, during, or subsequent to their pemetrexed therapy. in patients who received radiotherapy weeks or years previously
Cardiovascular events	Myocardial infarction and cerebrovascular events have been reported
Genetically damaging effects.	Sexually mature males are advised not to father a child during the treatment and up to 6 months thereafter. Women of childbearing potential must use effective contraception during treatment with pemetrexed.
Carboplatin	
Nephrotoxicity	Impairment of renal function is more likely in patients who have previously experienced nephrotoxicity as a result of cisplatin
Neuropathies	Peripheral neuropathy – more common in elderly patients and those previously treated with cisplatin.
Hepatobiliary toxicity	Raised liver function tests
Ocular	Rare reports of transient visual disturbances, which may include transient sight loss
Ototoxicity	Decreases in hearing acuity, consisting of high-frequency hearing loss In patients who have been previously treated with cisplatin and have developed hearing loss related to treatment, the hearing impairment may persist or worsen.
Additional side effects	Anaphylactic-like reactions to carboplatin have been reported Pulmonary fibrosis manifested by tightness of the chest and dyspnoea.

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Pre Cycle 3	Cycle 3	Cycle 4	Ongoing
Medical Assessment	X					X	At end of treatment
Nursing Assessment	X	X	X		X	X	Every cycle
On treatment review*				X			Before cycle 3
FBC	X	X	X		X	X	Every cycle
U&E & LFT & Mg	X	X	X		X	X	Every cycle
CrCl (Cockcroft and Gault)	X	X	X		X	X	Every cycle
CrCl (Wright formula if carboplatin)	X	X	X		X	X	Every cycle
Respiratory Rate							If clinically indicated
CT scan	X						End of treatment or as clinically indicated
Informed Consent	X						
Blood glucose	X						Repeat if clinically indicated
Blood pressure measurement	X						Repeat if clinically indicated
PS recorded	X	X	X		X	X	Every cycle
Toxicities documented	X	X	X		X	X	Every cycle
Weight recorded	X	X	X		X	X	Every cycle

*On treatment review: assessment by clinician with appropriate competencies to capture and communicate ongoing benefit including PS, toxicity, patient understanding, symptom control and clinical tumour response (imaging as required based upon assessment)

Dose Modifications and Toxicity Management:

Haematological Toxicity:

Proceed on day 1 if-

Plt ≥ 100 $x10^9$/L	ANC ≥ 1.0 $x10^9$/L

Delay 1 week on day 1 if-

Plt ≤ 99 $x10^9$/L	ANC ≤ 0.9 $x10^9$/L

These haematological guidelines assume that patients are well with good performance status, that other acute toxicities have resolved and the patient has not had a previous episode of neutropenic sepsis.

Non- Haematological Toxicity:
Hepatic impairment:

Cisplatin
No dose reduction necessary.

Pemetrexed
Pemetrexed undergoes limited hepatic metabolism and is primarily eliminated in the urine, with 70% to 90% of the administered dose being recovered unchanged in urine within the first 24 hours following administration. No relationships between AST, ALT or total bilirubin and pemetrexed pharmacokinetics were identified. However patients with hepatic impairment such as bilirubin >1.5 x upper limit of normal (ULN) and/or transaminase > 3.0 x ULN (hepatic metastases absent) or > 5.0 x ULN (hepatic metastases present) have not been specifically studied.

Carboplatin
Transient increases in liver enzymes have been reported. Probably no dose reduction necessary.

Renal impairment:

Cisplatin	
GFR (mL/min)	**Dose**
> 60	100%
45 to 59	75%
< 45	Consider Carboplatin: contact patient's consultant for advice.

Inadequate urine output (< 200mL/hr):

- Administering 500ml Sodium Chloride +/- furosemide 20 - 40mg - furosemide 20 – 40mg po may also be given if there is a positive fluid balance of 1.5 litres, a weight gain of 1.5kg or symptoms of fluid overload.

The patient should be asked to drink 2 litres of fluid in the 24hrs following treatment, and to contact the hospital if this is impossible because of problems e.g. nausea and vomiting.

Pemetrexed
GFR > 45mL/min 100% dose. If less than 45ml/min the consultant should be contacted as it is a clinical decision if pemetrexed is to continue. May be hazardous in severe renal impairment.

Carboplatin
Dose using Calvert equation: Dose = AUC*(25 + GFR) The carboplatin dose should not exceed 750mg (maximum creatinine clearance used to calculate dose=125ml/min). The initial dose does not need to be recalculated for subsequent cycles unless the patient is experiencing toxicity (including AKI). If CrCl <20ml/min contact consultant oncologist

Neurotoxicity:

If patient develops grade 2 neuropathy or ototoxicity, discuss with consultant. May consider 50% dose reduction in cisplatin. Patients with functional hearing loss should have cisplatin omitted; carboplatin AUC 3-5 can be substituted.

Cumulative: Dose related peripheral sensory neuropathy: Usually occurs after a cumulative dose. It can occur after treatment with cisplatin is completed, and is usually reversible, taking approx. 3 – 5 months to recovery.

Hypersensitivity:

Patients who have previously experienced Grade I or II Platinum HSR should be pre-medicated with 45 minutes prior to cisplatin/carboplatin:

- Hydrocortisone 100mg IV 30 minutes prior to cisplatin/carboplatin:
- Chlorphenamine 10 mg IV over 20 minutes

It should be strongly noted that patients who have severe reactions should not be re-challenged.

References:

- https://www.medicines.org.uk/emc
- Dosage Adjustment for Cytotoxics in Hepatic Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Hepatic Impairment (Version 3 - updated January 2009)
- Dosage Adjustment for Cytotoxics in Renal Impairment. January 2009 UCLH - Dosage Adjustment for Cytotoxics in Renal Impairment (Version 3 - updated January 2009)
- BNF available via: https://bnf.nice.org.uk/
- NICE TA 135: Pemetrexed for the treatment of malignancy pleural mesothelioma