Systemic Anti Cancer Treatment Protocol

Cisplatin with Pemetrexed and Pembrolizumab
Non squamous Non-Small Cell Lung Cancer

PROTOCOL REF: MPHACPPLU
(Version No: 1.2)

Approved for use in:

-Stage IIIB or IV non squamous non-small cell lung cancer

-1st line treatment for advanced/metastatic disease. Previous neoadjuvant/adjuvant treatment allowed as long as therapy was completed at least 6 months prior to diagnosis of recurrent locally advanced or metastatic disease.

-EGFR and ALK mutation testing must be complete and both are negative

-PDL-1 testing must have been attempted

-Patient must be registered on blueteq

-PS 0-1

Dosage:

Drug	Dose	Route	Frequency
Pembrolizumab	200 mg flat dose	IV Infusion	Every 21 days
Pemetrexed	500 mg/m^2	IV Infusion	Every 21 days
Cisplatin	75 mg/m^2	IV Infusion	Every 21 days

Repeat every 21 days for 4 cycles

Followed by:

Drug	Dose	Route	Frequency
Pembrolizumab	200 mg flat dose	IV Infusion	Every 21 days
Pemetrexed	500 mg/m^2	IV Infusion	Every 21 days

Total treatment duration is 2 years for Pembrolizumab (or a maximum of 35 cycles) or until disease progression or unacceptable toxicity, whichever occurs first. The duration of Pemetrexed is not limited to 2 years and can be continued until disease progression.

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, starting 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. Dexamethasone duration should be reduced to 3 days once the course of cisplatin is complete.

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

Extravasation risk:

Pemetrexed: Neutral

Cisplatin: Exfoliant

Pembrolizumab: treat symptomatically, no specific recommendations.

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	
	Pembrolizumab	**200mg**	IV	100mL sodium chloride 0.9%. Infused over 30 minutes in a non-pyrogenic line with a 0.2 micron filter
	Please change administration line before commencing pemetrexed			
	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		

Main Toxicities:

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. Please contact consultant as a switch to carboplatin may be considered.
Additional side effects	Anaphylactic-like reactions Nausea, anaemia, fatigue, neutropenia, decreased appetite, diarrhoea and vomiting. Mucositis (stomatitis, oesophagitis, pharyngitis, proctitis), bitter or metallic taste disturbance, alopecia and loss of fertility.
Pemetrexed	
Skin reactions	Pre-treatment with dexamethasone (or equivalent) can reduce the incidence and severity of skin reactions
Radiation pneumonitis **Radiation recall**	Cases of radiation pneumonitis and radiation recall have been reported in patients treated with radiation either prior, during, or subsequent to their pemetrexed therapy. Particular attention should be paid to these patients and caution exercised with use of other radio sensitising agents.
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.

Pembrolizumab	
Immune-Mediated Pneumonitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Immune-Mediated Colitis	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other Immune-Mediated Toxicities: Hypophysitis Nephritis Hyperthyroidism or Hypothyroidism Less frequently: Exfoliative dermatitis, uveitis, arthritis, myositis, pancreatitis, haemolytic anaemia	Monitor LFTs, biochemistry, cortisol and TFTs regularly Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Other adverse events: Fatigue, anaemia Cough, dyspnoea Nausea, decreased appetite Pruritis, rash Constipation, diarrhoea Arthralgia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
Laboratory abnormalities: Hyponatraemia, hypocalcaemia, hyperglycaemia, hypertriglyceridaemia	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Investigations and treatment plan

	Pre	Cycle 1	Cycle 2	Pre Cycle 3	Cycle 3	Cycle 4	Pre Cycle 5	Ongoing
Medical Assessment	X			X*			X	Every 6 to 12 weeks or as clinically indicated
Nursing Assessment	X	X	X		X	X		Every cycle
FBC	X	X	X		X	X		Every cycle
U&E & LFT (including ALT) & Mg	X	X	X		X	X		Every cycle
CrCl (Cockcroft and Gault)	X	X	X		X	X		Every cycle
TFTs (incl T3 and T4) and random cortisol	X	X	X		X	X		Every cycle
CRP		X	X		X	X		Every cycle
Respiratory Rate	X	X	X		X	X		Every cycle
CT scan	X						X	Every 3 months or as clinically indicated
Informed Consent	X							
Blood glucose	X	X	X		X	X		Every cycle
Blood pressure measurement	X	X	X		X	X		Every cycle
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

*Medical 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. Not recommended in severe liver impairment due to risk of pemetrexed induced liver dysfunction.

Pembrolizumab	
AST or ALT increase to 3 to 5 times the upper limit of normal (ULN) Bilirubin increase to 1.5 to 3 times ULN	Refer to Immuno-Oncology toxicity specific guidance for adverse event management
AST or ALT increase to greater than 5 times ULN Bilirubin increase to greater than 3 times ULN	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

In patient with liver metastasis with baseline AST or ALT at 3 to 5 times the ULN and increase by > 50% and lasting for more than one week	Refer to Immuno-Oncology toxicity specific guidance for adverse event management

Renal impairment:

Cisplatin	
GFR (mL/min)	**Dose**
> 60	100%
50 to 59	75%
< 50	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 (mL/min)	**Dose**
≥ 40	100%
30 to 39	80%
< 30	Not recommended. Consultant should be contacted. May be hazardous in severe renal impairment.

Pembrolizumab
No studies have been conducted on patients with severe renal impairment (eGFR <15ml/min). No dose adjustments are required for mild to moderate renal impairment.

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 substitution can be considered.

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:

- Hydrocortisone 100mg IV 30 minutes prior to cisplatin:
- 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
- Krens S D, Lassche, Jansman G F G A, et al. Dose recommendations for anticancer drugs in patients with renal or hepatic impairment. *Lancet Oncol* 2019; 20: e201–08.
- BNF available via: https://bnf.nice.org.uk/
- NEJM: Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. 378; 22. May 31st 2018
- NICE TA557: Pembrolizumab with pemetrexed and platinum for untreated, metastatic, non-squamous non-small-cell lung cancer. Published 10th January 2019