BC Cancer Protocol Summary for Treatment of Malignant Mesothelioma with Platinum and Pemetrexed

***Protocol Code**:* *LUMMPP*

***Tumour Group**:* *Lung*

***Contact Physician**:* *Dr. Christopher Lee*

ELIGIBILITY:
- Malignant mesothelioma
- ECOG performance status 0, 1 or 2

EXCLUSIONS:
- Prior chemotherapy

TESTS:
- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH
- Before each treatment: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH
- Weekly: CBC & differential, platelets during cycles 1 and 2; may be omitted in subsequent cycles

PREMEDICATIONS:
- Antiemetic protocol for highly emetogenic chemotherapy (see protocol SCNAUSEA)
- **Vitamin supplementation mandatory** starting at least 7 days prior to the first cycle, and to continue while on treatment, until 21 days after last Pemetrexed dose:
  - Folic Acid 0.4 mg PO OD
  - Vitamin B12 1000 µg IM every 9 weeks
- Prophylaxis for skin rash, Dexamethasone 4 mg PO BID for 3 days beginning the day before chemotherapy. (May proceed with chemotherapy even if patient has not taken the pre-treatment dexamethasone doses. Instruct patient to begin immediately.)

TREATMENT:

Drug	Dose	BC Cancer Administration Guideline
pemetrexed	500 mg/m^2	IV in NS 100 mL over 10 minutes†
CISplatin	75 mg/m^2	IV in NS 500 mL over 1 hour*
***Pre- and post-hydration protocol for high-dose CISplatin required according to institutional guidelines (eg, prehydration with 1 L NS over 1 hour, CISplatin in 500 mL NS with potassium chloride 20 mEq, magnesium sulfate 1 g and Mannitol 30 g)** **†Pemetrexed may be given anytime during the pre-hydration period[3]**		

- **Repeat every 21 days x 6 cycles**

DOSE MODIFICATIONS:

1. **HEMATOLOGY**

Based on day 1 counts:

ANC (x 10^9/L)		Platelets (x 10^9/L)	Dose
greater than or equal to 1.5	and	greater than or equal to 100	100%
less than 1.5	or	less than 100	**Delay**

Based on nadir counts (for Pemetrexed only):

ANC (x 10^9/L)		Platelets (x 10^9/L)	Pemetrexed Dose
greater than or equal to 0.5	and	greater than or equal to 50	100%
less than 0.5	and	greater than or equal to 50	75%
Any	and	less than 50	50%

2. **RENAL DYSFUNCTION**

Calculated Cr Clearance (mL/min)	CISplatin Dose	Pemetrexed Dose
greater than or equal to 60	100%	100%
45 to less than 60	80% CISplatin or go to CARBOplatin option	100%
less than 45	**Hold**	**Hold** regardless of type of platinum

3. **MUCOSITIS**

For next cycle:

Mucositis Grade	CISplatin dose	Pemetrexed dose
0 to 2	100%	100%
3 to 4	100%	50% previous dose*
*__Discontinue treatment after two dose reductions__		

4. **OTHER TOXICITIES**

For any other grade 3 or higher toxicity, delay treatment until toxicity resolves, then resume with 25% dose decrease if considered appropriate to resume by attending oncologist

Alternatively, CARBOplatin may be used instead of CISplatin:

DRUG	DOSE	BC Cancer Administration Guidelines
Pemetrexed	500 mg/m^2	IV in 100 mL NS over 10 minutes
CARBOplatin	Dose = AUC 5 x (GFR* + 25)	IV in 250mL NS over 30 minutes

- Repeat every 21 days x 6 cycles

*GFR may be determined by nuclear renogram or estimated by the Cockcroft formula, at the discretion of the attending physician:

$$\text{GFR} = \frac{\text{N x (140-age in years) x wt (kg)}}{\text{Serum creatinine (micromol/L)}} \qquad \text{N = 1.04 (women) or 1.23 (men)}$$

The estimated GFR should be capped at 125 mL/min when it is used to calculate the initial CARBOplatin dose. When a nuclear renogram is available, this clearance would take precedence.

PRECAUTIONS:

1. **Vitamin supplements**: Appropriate prescription of folic acid and vitamin B12 is essential. The incidence of adverse events such as febrile neutropenia related to pemetrexed is higher without vitamin supplementation.
2. **NSAIDs**: Concurrent nonsteroidal anti-inflammatory agents should be avoided as they may decrease the renal clearance of pemetrexed.
3. **Neutropenia**: Fever or other evidence of infection must be assessed promptly and treated aggressively.
4. **Renal Toxicity**: Nephrotoxicity is common with CISplatin. Encourage oral hydration. Avoid nephrotoxic drugs such as aminoglycoside antibiotics. Use caution with pre-existing renal dysfunction.
5. **Neurotoxicity**: CISplatin is neurotoxic and may have to be discontinued if functionally important neuropathy develops. Particular caution must be used in individuals with existing neuropathy.
6. **Ototoxicity**: CISplatin is ototoxic and its use must be cautioned in individuals with existing hearing loss.

Contact Dr. Christopher Lee or tumour group delegate at (604) 930-2098 or 1-800-523-2885 with any problems or questions regarding this treatment program.

REFERENCES:

1. Volgelzang NJ, Rusthoven JJ, Symanowski J, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol 2003;21:2636–44.
2. Hughes A, Calvert P, Azzabi A, et al. Phase I clinical and pharmacokinetic study of pemetrexed and carboplatin in patients with malignant pleural mesothelioma. J Clin Oncol 2002;20:3533-44.
3. Thodtmann R, Depenbrock H, Dumez H, et al. Clinical and pharmacokinetic phase I study of multitargeted antifolate (LY231514) in combination with cisplatin. J Clin Oncol 1999;17:3009-16.