BC Cancer Protocol Summary for First-Line Treatment of Advanced Non-Small Cell Lung Cancer with Platinum and Pemetrexed

***Protocol Code**:* *LUAVPP*

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

***Contact Physician**:* *Dr. Barb Melosky*

ELIGIBILITY:
- Advanced non-small cell lung cancer
- Restricted to disease of *non-squamous cell* histology
- May be used as second- or third-line therapy if prior treatment with immunotherapy or targeted agents
- ECOG performance status 0, 1 or 2
- NOTE: Use of LUAVPP as induction therapy precludes the use of second-line pemetrexed in the same patient

EXCLUSIONS:
- Prior chemotherapy for advanced non-small cell lung cancer

TESTS:
- Baseline: CBC & differential, platelets, creatinine, alkaline phosphatase, ALT, total bilirubin, LDH
  - C-reactive protein and albumin (optional, and results do not have to be available to proceed with first treatment)
- 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 mcg 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 100 mL NS over 10 minutes†
CISplatin	75 mg/m^2	IV in 500 mL NS over 1 hour*

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***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 4 to 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
0-2	100%	100%
3-4	100%	50% previous dose*
***Discontinue treatment after two dose reductions**		

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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 100 to 250 mL NS over 30 minutes

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

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

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.

- Repeat every 21 days x 6 cycles

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. Barb Melosky or tumour group delegate at (604) 877-6000 or 1-800-663-3333 with any problems or questions regarding this treatment program.

REFERENCES:

1. Scagliotti GV, Parikh P, von Pawel J, et al. Phase III study comparing cisplatin plus gemcitabine with cisplatin plus pemetrexed in chemotherapy-naive patients with advanced-stage non-small-cell lung cancer. J Clin Oncol 2008;26(21):3543-51.
2. Syrigos KN, Vansteenkiste J, Parikh P, et al. Prognostic and predictive factors in a randomized phase III trial comparing cisplatin-pemetrexed versus cisplatin-gemcitabine in advanced non-small-cell lung cancer. Ann Oncol 2010;21(3):556-61.
3. Ciuleanu T, Brodowicz T, Zielinski C, et al. Maintenance pemetrexed plus best supportive care versus placebo plus best supportive care for non-small-cell lung cancer: a randomised, double-blind, phase 3 study. Lancet 2009;374:1432-40.

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