
**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
- Patients who have relapsed within 12 months of completing adjuvant chemotherapy with LUAJPP

**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 8 to 12 mg PO prior to treatment, then 4 mg PO every 12 hours for 4 doses

**TREATMENT:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BC Cancer Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>pemetrexed</td>
<td>500 mg/m²</td>
<td>IV in 100 mL NS over 10 minutes</td>
</tr>
<tr>
<td>CISplatin</td>
<td>75 mg/m²</td>
<td>IV in 500 mL NS over 1 hour</td>
</tr>
</tbody>
</table>

*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

- Repeat every 21 days x 4 to 6 cycles
DOSE MODIFICATIONS:

1. HEMATOLOGY
   Based on day 1 counts:
   
<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 1.5 and greater than or equal to 100</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>less than 1.5 or less than 100</td>
<td>Delay</td>
<td></td>
</tr>
</tbody>
</table>

   Based on nadir counts (for Pemetrexed only):
   
<table>
<thead>
<tr>
<th>ANC (x 10^9/L)</th>
<th>Platelets (x 10^9/L)</th>
<th>Pemetrexed Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 0.5 and greater than or equal to 50</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>less than 0.5 and greater than or equal to 50</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>Any and less than 50</td>
<td>50%</td>
<td></td>
</tr>
</tbody>
</table>

2. RENAL DYSFUNCTION

<table>
<thead>
<tr>
<th>Calculated Cr Clearance (mL/min)</th>
<th>CISplatin Dose</th>
<th>Pemetrexed Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 60</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>45 to less than 60</td>
<td>80% CISplatin or go to CARBOplatin option</td>
<td>100%</td>
</tr>
<tr>
<td>less than 45</td>
<td>Hold</td>
<td>Hold regardless of type of platinum</td>
</tr>
</tbody>
</table>

3. MUCOSITIS
   For next cycle:
   
<table>
<thead>
<tr>
<th>Mucositis Grade</th>
<th>CISplatin dose</th>
<th>Pemetrexed dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 2</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>3 to 4</td>
<td>100%</td>
<td>50% previous dose*</td>
</tr>
</tbody>
</table>
   
   *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:

<table>
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<tr>
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<th>BC Cancer Administration Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemetrexed</td>
<td>500 mg/m²</td>
<td>IV in 100 mL NS over 10 minutes</td>
</tr>
<tr>
<td>CARBOplatin</td>
<td>Dose = AUC 5 x (GFR* + 25)</td>
<td>IV in 100 to 250 mL NS over 30 minutes</td>
</tr>
</tbody>
</table>

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

\[
GFR = \frac{N \times (140 - \text{age in years}) \times \text{wt (kg)}}{\text{Serum creatinine (micromol/L)}}
\]

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.

- 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:**