BCCA Protocol Summary for Therapy of Relapsed Multiple Myeloma Using Lenalidomide with Dexamethasone

Protocol Code: UMYLDREL
Tumour Group: Lymphoma, Leukemia/BMT
Contact Physician: Dr. Kevin Song
Contact Pharmacist: Linda Hamata

ELIGIBILITY:
- For the treatment of multiple myeloma in patients who received at least one prior therapy, including patients who relapse after maintenance lenalidomide (UMYLENMTN)
- A BC Cancer Agency “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment
- May be used in combination with cyclophosphamide, dexamethasone or prednisone
- Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca)

EXCLUSIONS:
- Pregnant or lactating women
- Platelet count less than 30 x 10^9/L may be considered a relative contraindication.
- If absolute neutrophil count (ANC) less than 1.0 x 10^9/L may be considered a relative contraindication. Consider giving filgrastim
- Known hypersensitivity to lenalidomide, pomalidomide or thalidomide

TESTS:
- Baseline (required before first treatment): CBC & diff, platelets, creatinine, LFTs (bilirubin, AST, ALT). If female of child-bearing potential (FCBP): Confirm negative pregnancy test results obtained 7 to 14 days and 24 hours prior to initial prescription. Baseline (required, but results do not have to be available to proceed with first treatment): calcium and serum protein electrophoresis, HBsAg, HBCoreAb, TSH
- Every 2 weeks for the first 4 cycles then may reduce frequency to every 4 weeks: CBC and diff, platelets, creatinine, calcium
- Every 4 weeks (required before treatment): CBC and diff, platelets, creatinine; if female of childbearing potential: pregnancy test (blood)
- Every 4 weeks (required, but results do not have to be available to proceed with treatment): calcium and serum protein electrophoresis; free light chain if clinically indicated
- Every three months (required, but results do not have to be available to proceed with treatment): T3, T4, TSH
- If clinically indicated: bilirubin, AST, ALT, see Precautions #2

PREMEDICATIONS:
None
TREATMENT:

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>lenalidomide</td>
<td>25 mg once daily for 21 days (d 1-21)</td>
<td>PO, in the evening may be preferred</td>
</tr>
<tr>
<td>dexamethasone</td>
<td>*40 mg once daily on days 1, 8, 15 and 22</td>
<td>PO, in the morning may be preferred</td>
</tr>
</tbody>
</table>

* Dose may vary dependent on tolerability and co-morbidities

- Patients over 75 years of age: consider using dexamethasone 20 mg
- predniSONE may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance.

Repeat every 28 days until progression of the myeloma or unacceptable toxicity

OTHER OPTIONS FOR DEXAMETHASONE DOSING

**Option A:**
Oral dexamethasone 20 mg or 40 mg daily on days 1-4, 9-12, 17-20 x 4 cycles; then 20 mg or 40 mg daily on days 1-4 only for subsequent cycles. The dose should be adjusted based upon toxicity and patient tolerance.

**Option B:**
Prednisone may be substituted for patient or physician preference, in a variety of regimens based upon toxicity and patient tolerance.

**Option C:**
No dexamethasone. Dexamethasone may need to be avoided in certain patients who are intolerant or have difficulty with side-effects. It is expected that the response will be inferior using lenalidomide alone. Dexamethasone may be added for non-response.

Repeat every 28 days until progression of the myeloma or unacceptable toxicity
LENALIDOMIDE DOSE MODIFICATIONS:
Fatigue may respond to dose reduction
NB: Use one of the 25 mg, 20 mg, 15 mg, 10 mg or 5 mg or 2.5 mg capsules for dosing.
Currently there is no evidence to support the use of other dosing regimens (i.e., there is no
clinical reason or research available to support the use of a combination of lenalidomide
capsules for dosing, however the use of such dosing does have significant budgetary
implications).

Dexamethasone should continue to be taken even if lenalidomide is held due to a dose limiting
toxicity.

<table>
<thead>
<tr>
<th>Dose Levels</th>
<th>Lenalidomide on Days 1–21 of Every 28-Day Cycle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard dose</td>
<td>25 mg on Days 1-21</td>
</tr>
<tr>
<td>Dose level -1</td>
<td>20 mg on Days 1-21</td>
</tr>
<tr>
<td>Dose level -2</td>
<td>15 mg on Days 1-21</td>
</tr>
<tr>
<td>Dose level -3</td>
<td>10 mg on Days 1-21</td>
</tr>
<tr>
<td>Dose level -4</td>
<td>5 mg on Days 1-21</td>
</tr>
<tr>
<td>Dose level -5</td>
<td>2.5 mg on Days 1-21</td>
</tr>
</tbody>
</table>
1. **Hematological Day 1**

<table>
<thead>
<tr>
<th>ANC (x10^9/L)</th>
<th>Platelets (x10^9/L)</th>
<th>1st Event Dose</th>
<th>2nd Event Dose</th>
<th>3rd Event Dose</th>
<th>4th Event Dose or subsequent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than or equal to 1.0 and Greater than or equal to 30</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>Less than 1† or Less than 30</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed</td>
<td></td>
</tr>
</tbody>
</table>

* Follow hematology weekly and delay until ANC greater than or equal to 1.0 x 10^9/L and platelets greater than or equal to 30 x 10^9/L and no evidence of hemostatic failure (i.e., bleeding or petechiae)
† Consider G-CSF if clinically indicated and G-CSF is available

**Day 15:**

For Cycles 1-4: Physician will monitor Day 15 bloodwork and physician will be responsible to advise patient on dose adjustment based on ANC and platelets. Note: For ANC less than 1.0 x 10^9/L or platelets less than 30 x 10^9/L, omit lenalidomide for remainder of cycle; restart on Day 1 of next cycle if counts have recovered; consider decreasing by one dose level when dosing resumed.

2. **Renal dysfunction:**

<table>
<thead>
<tr>
<th>Estimated GFR (eGFR)* or Creatinine clearance (mL/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than or equal to 60</td>
<td>25 mg†</td>
</tr>
<tr>
<td>30-59</td>
<td>10 mg‡</td>
</tr>
<tr>
<td>less than 30, not requiring dialysis</td>
<td>15 mg every other day for 21 days, then rest for 7 days (i.e. 28-day cycle)</td>
</tr>
<tr>
<td>less than 30, dialysis dependent</td>
<td>5 mg† (administer after dialysis on dialysis day)</td>
</tr>
</tbody>
</table>

* as reported in patient’s laboratory report
† dosing for 21 days (d 1-21) of each 28-day cycle
†dose can be escalated to 15 mg after 2 cycles if patient is not responding to treatment and is tolerating the drug; may consider escalating to 25 mg if patient continues to tolerate the drug.

3. Non-hematological/Non-renal

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>1st occurrence</th>
<th>2nd occurrence</th>
<th>3rd occurrence</th>
<th>4th or subsequent occurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 3 or greater exfoliative rash, SJS, TEN</td>
<td>Discontinue</td>
<td></td>
<td></td>
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<tr>
<td>Pneumonitis</td>
<td>For suspected pneumonitis, hold and investigate; discontinue if confirmed</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 3-4 (any other toxicity)</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed at next cycle</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed at next cycle</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed at next cycle</td>
<td>Delay* then consider decreasing by one dose level when dosing resumed at next cycle</td>
</tr>
</tbody>
</table>

*Stop treatment immediately and delay until toxicity resolved to grade 0-2

**PRECAUTIONS:**

1. **Teratogenicity:** If lenalidomide is taken during pregnancy, it may cause severe birth defects or death to the fetus. Lenalidomide should never be used by females who are pregnant or who could become pregnant while taking the drug. Even a single dose taken by a pregnant woman may cause birth defects.
2. **Hepatotoxicity:** Hepatic failure, including fatal cases, has been reported in multiple myeloma patients treated with lenalidomide in combination with dexamethasone during post-marketing. The mechanism of severe drug-induced hepatotoxicity is unknown. Pre-existing viral liver disease, elevated baseline liver enzymes and concomitant medications may be risk factors. Stop lenalidomide upon elevation of liver enzymes. After return to baseline values, treatment at a lower dose may be considered.
3. **Constipation:** Patients should be warned that constipation may occur in patients taking lenalidomide.
4. **Fatigue:** Patients should be warned that lenalidomide may cause fatigue.
5. **Hypothyroidism:** the use of lenalidomide may result in hypothyroidism. Thyroid function tests should be repeated every 3 months. Treatment with thyroid replacement should be considered even for subclinical hypothyroidism. Lenalidomide can be continued if hypothyroidism can be easily managed.
6. **Venous thrombosis/embolism:** Lenalidomide with dexamethasone is known to increase the risk for thromboembolic disease. **Aspirin 81 mg** oral daily should be considered in all patients. For those with higher risk of thromboembolic disease full anti-coagulation should be considered.

7. **Hepatitis B Reactivation:** All myeloma patients should be tested for both HBsAg and HBeAg. If either test is positive, such patients should be treated with Lamivudine 100 mg/day orally, for the entire duration of chemotherapy and for six months afterwards. Such patients should also be monitored with frequent liver function tests and hepatitis B virus DNA at least every two months. If the hepatitis B virus DNA level rises during this monitoring, management should be reviewed with an appropriate specialist with experience managing hepatitis and consideration given to halting chemotherapy.

8. **Skin Rashes:** Lenalidomide may cause skin rashes although in general they are not severe. Minor rashes can be treated with diphenhydramine and/or steroid creams and lenalidomide can be continued. Moderate rashes may require holding lenalidomide until resolution of the rash. For more severe rashes (greater than or equal to Grade 3: severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering greater than or equal to 50% BSA) lenalidomide should be discontinued.

9. **Second Primary Malignancies (SPM):** In clinical trials of previously treated multiple myeloma patients, for those receiving lenalidomide with dexamethasone, the incidence rate of SPM was increased (3.98 per 100 person years) compared to controls (1.38 per 100 person years). The non-invasive SPM were basal cell or squamous cell skin cancers, while most of the invasive SPM were solid tumour malignancies. The risk of occurrence of SPM must be taken into account before initiating treatment with lenalidomide in relapsed multiple myeloma patients. Physicians should carefully evaluate patients before and during treatment using standard cancer screening for occurrence of secondary primary malignancies and institute treatment as indicated.

Call Dr. Kevin Song (Leukemia/BMT) or Dr Laurie Sehn (Lymphoma) or tumour group delegate with any problems or questions regarding this treatment program. (Leukemia/BMT at (604) 875-4863 or after hours (604) 875-4111; Lymphoma at (604) 877-6000 or 1-800-663-3333)

**References:**