BCCA Protocol Summary for the Treatment of Multiple Myeloma Using Melphalan, predniSONE and Thalidomide

Protocol Code
UMYMPT

Tumour Group
Lymphoma and Leukemia/BMT

Contact Physician
Dr. Kevin Song

Contact Pharmacist
Linda Hamata

ELIGIBILITY:
• Previously untreated multiple myeloma patients who are not eligible for stem cell transplant
• Patients not eligible for treatment with melphalan, prednisone and weekly bortezomib (MYMPBOR)
• May be used in combination with cyclophosphamide, dexamethasone, melphalan or predniSONE
• A BC Cancer Agency “Compassionate Access Program” request with appropriate clinical information for each patient must be approved prior to treatment
• Registration of the prescribing physician and patient with the RevAid Program (www.RevAid.ca)

EXCLUSIONS:
• Pregnant or lactating women
• Absolute neutrophil count (ANC) less than 1 x 10^9/L (for melphalan)
• Platelet count less than 50 x 10^9/L (for melphalan)
• Caution in patients with known hypersensitivity to lenalidomide or thalidomide
• Grade 2 peripheral neuropathy (sensory alteration or symptomatic weakness interfering with function)

TESTS:
• Baseline (required before first treatment): CBC and diff, platelets, creatinine, bilirubin, AST, ALT. If female of child bearing potential: pregnancy test (blood) or evidence of hysterectomy
• Baseline (required, but results do not have to be available to proceed with first treatment; results must be checked before proceeding with cycle 2): serum protein electrophoresis, 24 hour urine collection for protein and Bence-Jones protein, urine protein electrophoresis, calcium, skeletal survey X-rays, HBsAg, HBcoreAg
• Before each treatment: CBC and diff, platelets, creatinine. If female of child bearing potential (FCBP): pregnancy test (blood) is required every 28 days while on thalidomide. NB: For FCBP, the pregnancy test must be within 7 days of dispensing thalidomide and a maximum of 28 days thalidomide supply may be dispensed at one time, as per the RevAid® Program.
• Before each treatment (required, but results do not have to be available to proceed with treatment) serum protein electrophoresis (if paraprotein detected originally), calcium.
• If clinically indicated: skeletal survey X-rays (at least annually)
• Every 3 months: T3, T4, TSH

PREMEDICATIONS: None

SUPPORTIVE MEDICATIONS:
If HBsAg or HBcoreAb positive, start lamiVUDine 100 mg/day PO for the duration of chemotherapy and for six months afterwards.

TREATMENT: Cycle length 42 days

For Patients less than 75 years of age

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>BCCA Administration Guideline</th>
</tr>
</thead>
<tbody>
<tr>
<td>melphalan</td>
<td>9 mg/m²/day on days 1-4*</td>
<td>PO</td>
</tr>
<tr>
<td>predniSONE</td>
<td>100 mg/day on days 1-4</td>
<td>PO, in the morning may be preferred</td>
</tr>
<tr>
<td>thalidomide</td>
<td>100 mg daily for first cycle,</td>
<td>PO, once daily at bedtime. If necessary,</td>
</tr>
<tr>
<td></td>
<td>then may gradually increase by 50 mg per cycle to a maximum of 200 mg daily</td>
<td>the total daily dose can be divided into as many as 4 doses to improve patient tolerance.</td>
</tr>
</tbody>
</table>

*Round dose to nearest 2 mg

Repeat every 42 days to a maximum of 12 cycles.

Discontinue melphalan and prednisone when there is evidence of toxicity or progression or when no further response is detectable for at least two cycles (usually established by plateau of monoclonal protein level). Continue with thalidomide until there is evidence of unacceptable toxicity or progression for a total of 12 (42 day) cycles.
For Patients 75 years of age or greater

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DOSE MODIFICATIONS: apply on the day of treatment

1. Hematological

   Melphalan

<table>
<thead>
<tr>
<th>ANC (x10⁹ /L)</th>
<th>Platelets (x10⁹ /L)</th>
<th>Dose (Melphalan)</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than 3</td>
<td>greater than 200</td>
<td>Increase by 2 mg/day</td>
</tr>
<tr>
<td>1-3</td>
<td>greater than or equal to 100</td>
<td>100% of previous dose</td>
</tr>
<tr>
<td>less than 1</td>
<td>less than 100</td>
<td>Check CBC &amp; diff weekly, resume treatment when ANC is greater than 1 and platelets greater than 100. After second occurrence consider reducing dose of melphalan to 75 %*</td>
</tr>
</tbody>
</table>

*Round dose to nearest 2 mg
Thalidomide and prednisone: no adjustment is necessary
2. Peripheral Neuropathy

Thalidomide

<table>
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<th>Severity of Peripheral Neuropathy Signs</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Grade 1 (paresthesia and/or loss of reflexes) without pain or loss of function</td>
<td>100 %, but monitor patient and consider a dose reduction* if symptoms worsen</td>
</tr>
<tr>
<td>Grade 1 with pain, or Grade 2 (with pain interfering with function, but not with activities of daily living)</td>
<td>Reduce by 50%</td>
</tr>
<tr>
<td>Grade 3 and 4</td>
<td>discontinue</td>
</tr>
</tbody>
</table>

*50 mg, 100 mg, 200 mg capsules available

3. Renal Failure

For Melphalan, dose modification is necessary for renal failure.

<table>
<thead>
<tr>
<th>Creatinine clearance (mL/min)</th>
<th>Melphalan Dose</th>
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<tr>
<td>Greater than 50</td>
<td>100 %</td>
</tr>
<tr>
<td>10-50</td>
<td>75 %</td>
</tr>
<tr>
<td>Less than 10</td>
<td>50 %</td>
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</table>

Calculated creatinine clearance = \(N \times \frac{140 - \text{Age}}{\text{weight (kg)}} \times \text{Serum Creatinine (micromols/L)}\)

\(N = 1.04\) (Females) and \(1.23\) (Males)

Thalidomide and Prednisone: no adjustment is necessary.

4. Other Non-hematological dose modifications

For Thalidomide: somnolence and/or constipation may respond to dose reduction.

For Prednisone: dose may need to be decreased or prednisone may need to be avoided in certain patients who are intolerant or have difficulties with side-effects. It is expected that the response will be inferior.

PRECAUTIONS:

1. Neutropenia: Fever or other evidence of infection must be assessed promptly and treated aggressively.

2. Teratogenicity: If thalidomide is taken during pregnancy, it causes severe birth defects or death to the fetus. Thalidomide 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 can cause birth defects. The critical period occurs between 20 and 40 days of gestation. The defects seen have included amelia,
phocomelia, hypoplasia of the bones and absence of bones, anotia, microtia, facial palsy, anophthalmos, microphthalmos, congenital heart defects, and gastrointestinal and renal anomalies.

3. **Peripheral Neuropathy**: Permanent peripheral neuropathy may occur. Clinical symptoms may include symmetrical sensorimotor neuropathy, painful paresthesia in the hands and feet, distal hypoesthesia, proximal weakness in the lower limbs, slight postural tremor, leg cramps, absent ankle jerks and redness of the palms. Thalidomide should be discontinued or substantially reduced in dose if signs and symptoms of peripheral neuropathy occur.

4. **Constipation**: Patients should be warned that constipation is common and difficult to manage in patients taking thalidomide. Thalidomide should be given very cautiously to patients already taking narcotic analgesics. Patients should follow the same anti-constipation measures used by those taking large doses or narcotic analgesics to prevent constipation.

5. **Somnolence**: Patients should be warned that thalidomide causes somnolence and that they should avoid driving unless fully alert. They should not drive at all if also taking narcotics or alcohol.

6. **Hypothyroidism**: the use of thalidomide may result in hypothyroidism. Thyroid function tests should be repeated every 3 months. Treatment with thyroid replacement should be considered even for subclinical hypothyroidism. Thalidomide can be continued if hypothyroidism can be easily managed.

7. **Venous thrombosis/embolism**: Thalidomide with melphalan and prednisone is known to increase the risk for thromboembolic disease. *Aspirin 81mg* oral daily should be considered in all patients. For those with higher risk of thrombo-embolic disease full anti-coagulation should be considered.

8. **Skin Rashes**: Thalidomide may cause skin rashes although in general these are not severe. Minor rashes can be treated with diphenhydramine and/or steroid creams and thalidomide can be continued. Moderate rashes may require holding thalidomide 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) thalidomide should be discontinued.

9. **Hepatitis B Reactivation**: All lymphoma patients should be tested for both HBsAg and HBcAb. If either test is positive, corticosteroids should be omitted from treatment and such patients should be treated with lamivudine during 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.
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

Date activated: 1 Apr 2009
Date revised: 1 Oct 2016 (Eligibility clarified)
References: