

BCCA Protocol Summary for the Treatment of Systemic Light-chain (AL) Amyloidosis and Multiple Myeloma Using Cyclophosphamide, Thalidomide and Dexamethasone

Protocol Code *UMYCTD*

Tumour Group *Lymphoma and Leukemia/BMT*

Contact Physician *Dr. Kevin Song*

Contact Pharmacist *Linda Hamata*

ELIGIBILITY:

- All patients with primary AL amyloidosis and myeloma with/without secondary amyloidosis who are judged candidates for chemotherapy.
- A BCCA "[Compassionate Access Program](#)" (CAP) request must be completed and approved.
- [Registration of the prescribing physician and patient in the RevAid Program \(1-888-738-2431 or \[www.RevAid.ca\]\(http://www.RevAid.ca\)\)](#)
- BCCA does not fund thalidomide at this time, Contact the RevAid Program (above) for drug access and funding options.

EXCLUSIONS:

- Pregnant or lactating women
- Absolute neutrophils count (ANC) less than $1 \times 10^9/L$
- Platelets count less than $50 \times 10^9/L$
- Known hypersensitivity to lenalidomide or thalidomide
- Grade 2 peripheral neuropathy (sensory alteration or symptomatic weakness interfering with function)
- Amyloidosis not caused by a plasma cell dyscrasia

TESTS:

- Baseline (required before first treatment): CBC and diff, platelets, serum protein electrophoresis, serum free light chain level, 24 hour urine collection for protein and Bence-Jones protein, urine protein electrophoresis, calcium, creatinine. 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): skeletal survey X-rays, HBsAg, HBcoreAg
- Before each treatment: CBC and diff, platelets, serum protein electrophoresis (if paraprotein detected originally), serum free light chain level (if appropriate), calcium, creatinine. If female of child bearing potential: pregnancy test (blood)
- If clinically indicated: skeletal survey X-rays (at least annually)
- Every 3 months: T3, T4, TSH

PREMEDICATIONS:

None

TREATMENT:

Cyclophosphamide, Thalidomide and Dexamethasone (CTD)

Drug	Dose	BCCA Administration Guideline
Cyclophosphamide	500 mg weekly	PO
Thalidomide	100 mg daily. Increase to 200 mg daily after 4 weeks as tolerated	PO
Dexamethasone	40 mg daily days 1-4, 9-12	PO

Repeat every 21 days. Treatment is given until a stable clonal response is achieved or patient confirmed to be unresponsive; maximum up to 12 cycles if tolerated.

Attenuated CTD, for elderly or poor-risk patients (e.g., greater than 70 years, patients with heart failure, or significant fluid overload).

Drug	Dose	BCCA Administration Guideline
Cyclophosphamide	500 mg days 1, 8, 15	PO
Thalidomide	50 mg daily. Increase by 50 mg every 4 weeks as tolerated until 200 mg daily	PO
Dexamethasone	40 mg daily days 1-4, 15-18	PO

Repeat every 28 days. Treatment is given until a stable clonal response is achieved or patient confirmed to be unresponsive; maximum up to 12 cycles if tolerated.

DOSE MODIFICATIONS: apply on the day of treatment**1. Hematological**

Cyclophosphamide:

ANC ($\times 10^9$ /L)	Platelets ($\times 10^9$ /L)	Dose (cyclophosphamide)
greater than 1.2	greater than 80	100%
less than or equal to 1.2	less than or equal to 80	Delay until recovery

*Round to nearest 25 mg dose

Thalidomide, and dexamethasone: no adjustment is necessary

2. Renal dysfunction: Dose modification required for cyclophosphamide. Refer to BCCA Cancer Drug Manual. No adjustment required for thalidomide or dexamethasone.

3. For thalidomide, somnolence, constipation or peripheral neuropathy may respond to dose reduction.

4. Dexamethasone dose may need to be decreased or dexamethasone 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 of 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 cyclophosphamide and dexamethasone 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 it is 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 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.

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 December 2011 (thalidomide access and protocol contact information)

References^{1,2}:

1. Wechalekar AD, Goodman HJ, Lachmann HJ, Offer M, Hawkins PN, Gillmore JD. Safety and efficacy of risk-adapted cyclophosphamide, thalidomide, and dexamethasone in systemic AL amyloidosis. *Blood*. 2007;109:457-464.
2. Palumbo A, Rajkumar SV, Dimopoulos MA, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. *Leukemia*. 2008;22:414-423.