BC Cancer Protocol Summary for Therapy of Myelodysplastic Syndrome using Lenalidomide

Protocol Code	*LKMDSL*
Tumour Group	*Leukemia/BMT*
Contact Physician	*Dr. Tom Nevill*

ELIGIBILITY:

- Transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndrome (MDS) associated with a deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities.

EXCLUSIONS:

- Contraindicated in patients who are hypersensitive to lenalidomide or to thalidomide.
- Lenalidomide is structurally similar to thalidomide, a known teratogen, and is contraindicated in pregnant women and women at risk of becoming pregnant.
- Contraindicated in breast feeding women.
- If ANC less than 0.5, Platelets less than 30 $x10^9$/L (if Platelets 30-50, consider giving platelet transfusion and if increments to greater than 50, start Lenalidomide)

TESTS:

- Baseline:
  - Bone Marrow aspiration and cytogenetic testing.
  - CBC and Differential, platelets, serum creatinine, bilirubin, ALT, Alk Phos
  - If premenopausal female: lab based pregnancy test x 2 prior to initiation of treatment. Test #1 – 7-14 days prior, Test #2 – 24 hour prior
  - TSH
- Weekly x 1 month: CBC and differential, platelets, serum creatinine; if premenopausal female, pregnancy test.
- Monthly after 1st month therapy: CBC and Differential, platelets, serum creatinine**,** bilirubin, ALT, Alk Phos, pregnancy test (if premenopausal)
- Every 3 months after 1st month therapy: TSH, T3, T4
- 4 weeks after discontinuing lenalidomide – pregnancy test
- regular clinical assessments and grading of rash, diarrhea, fatigue and respiratory symptoms

PREMEDICATIONS:

- Consider therapeutic anticoagulation with low molecular weight heparin (LMWH) in patients with previous deep vein thrombosis and/or pulmonary embolism; maintain platelets greater than 50 x 10^9/L while on therapeutic LMWH (see Precautions)

TREATMENT:

Drug	Dose*	BC Cancer Administration Guideline
lenalidomide	10 mg once daily for 21 days (d 1-21)	PO

- Repeat every 28days until loss of response (progression of MDS or need for RBC transfusion)
- Discontinue if no response after 4 cycles.

  * Select dose carefully and closely monitor renal function in the elderly due to the potential for decreased renal function. The incidence of serious and non-serious adverse events is significantly higher in patients greater than 65 years (constipation, confusion, dyspnea, atrial fibrillation).

DOSE MODIFICATIONS:

1. Hematological:

A. If myelosuppression develops **within 4** weeks of starting treatment at **10 mg daily**

Baseline			During therapy			Action
Platelets ($X10^9$/L)		**ANC ($X10^9$/L)**	**Platelets ($X10^9$/L)**		**ANC ($X10^9$/L)**	
greater than or equal to 100	and / or	greater than or equal to 1.0	Less than 50	and / or	Less than 0.75	Hold. Restart at 5 mg/day when platelets greater than or equal to 50 and ANC greater than or equal to 1.0
60 to less than 100		less than 1.0	50% of baseline		Less than 0.50	Hold. Restart at 5 mg/day when platelets greater than or equal to 50 and ANC greater than or equal to 0.5
less than 60						Hold. Restart at 5 mg/day when platelets greater than or equal to 30 and ANC greater than or equal to 0.5

B. If myelosuppression develops **after 4** weeks of starting treatment at **10 mg daily**

During therapy			Action
Platelets ($X10^9$/L)		**ANC ($X10^9$/L)**	
less than 30, or less than 50 requiring transfusion	and / or	less than 0.5 for 7 days or longer, or with fever (≥38.5°C)	Hold. Restart at 5 mg/day when platelets greater than or equal to 30 and ANC greater than or equal to 0.5

C. If myelosuppression develops **after 4** weeks of starting treatment at **5 mg daily**

During therapy			Action
Platelets ($X10^9$/L)		**ANC ($X10^9$/L)**	
less than 30, or less than 50 requiring transfusion	and / or	less than 0.5 for 7 days or longer, or with fever (≥38.5°C)	Hold. Restart at 5 mg **EVERY OTHER DAY** when platelets greater than or equal to 30 (without bleeding) and ANC greater than or equal to 0.5

2. **Renal dysfunction:**

Creatinine clearance (mL/min)	Dose*
greater than or equal to 60	10 mg/d
30-59	5 mg/d
less than 30, not requiring dialysis	5 mg every other day
less than 30, dialysis dependent	5 mg three times weekly (administer after dialysis)

* dosing for 21 days (d 1-21) of each 28-day cycle

3. **Hepatic failure,** sometimes fatal, has occurred in patients receiving lenalidomide in combination with dexamethasone. Acute hepatic failure, toxic hepatitis, cytolytic hepatitis, and cholestatic hepatitis have been reported. The mechanism of this reaction is unknown; however, pre-existing viral liver disease, elevated baseline liver enzymes, and concomitant medications may be risk factors. Periodic monitoring of liver enzymes is recommended. Hold lenalidomide upon elevation of liver enzymes; resumption of treatment at a lower dose may be considered after liver enzymes have returned to baseline.

PRECAUTIONS:

1. **Neutropenia (grade 3-4)**: occurs in 62% of patients. Fever or other evidence of infection must be assessed promptly and treated aggressively. Refer to BC Cancer Febrile Neutropenia Guidelines.
2. **Thrombocytopenia (grade 3-4): occurs in** 53% of patients. Monitor for signs of bleeding.
3. **Thromboembolism:** occurs in 3-5% of MDS patients receiving lenalidomide as a single agent but is more frequent in myeloma patients when lenalidomide is used in combination therapy with dexamethasone. Use of lenalidomide and Erythropoietin together in MDS patients is not recommended. Also see Premedications for use of LMWH.
4. **Cardiac Toxicity**: Edema, weight gain (24%), cardiac failure (3%), Hypertension (7%), chest pain (6%)
5. **Hypersensitivity**: Rarely, hypersensitivity pneumonitis-like syndrome has been reported with lenalidomide use. In the case of unexpected respiratory symptoms such as dyspnea on exertion, crackles on physical examination, radiological bilateral ground-glass opacities and non-resolving pneumonia, lenalidomide should be discontinued until further investigation excludes hypersensitivity pneumonitis-like syndrome.
6. **Interactions:** lenalidomide increases digoxin concentration. It also increases the risk of bleeding in patients taking anticoagulants, NSAIDS, platelet inhibitors, thrombolytic agents, etc.

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

References:

1. 1. List A, Kurtin S, Roe DJ, et al. Efficacy of lenalidomide in myelodysplastic syndromes. N Engl J Med 2005;352(6):549-57.
2. 2. List A, Dewald G, Bennett J, et al. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. N Engl J Med 2006;355(14):1456-65.
3. 3. List AF, Dewald GW, Bennett JM, et al. Long-term clinical benefit of lenalidomide (Revlimid) treatment in patients with myelodysplastic syndrome and chromosome deletion 5q. ASH Annual Meeting Abstracts 2006;108(11):251-.
4. 4. Celgene REVLIMID product monograph. Oakville, Ontario; 30 June, 2011
5. Celgene Inc. Health Canada Endorsed Important Safety Information on REVLIMID® (lenalidomide) - Association of REVLIMID® (lenalidomide) with the risk of hepatotoxicity. Health Canada, 27 December 2013. Available at: http://www.hc-sc.gc.ca/dhp-mps/medeff/advisories-avis/prof/. Accessed 31 December 2013.
6. Cancer Care Ontario. Lenalidomide Monograph. September 2018. Available at: https://www.cancercareontario.ca/en/drugformulary/drugs/lenalidomide. Accessed on: 14 February 2019.