



Lenalidomide in multiple myeloma— a practice guideline

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ABSTRACT

Background

Promising new drugs such as lenalidomide, an immunomodulatory agent, are available for the treatment of multiple myeloma. We describe the process of creating a provincial guideline for the use of lenalidomide, alone or in combination with other drugs, in relapsed, refractory, or newly diagnosed disease (including smoldering and symptomatic patients, and candidates and non-candidates for transplant) and in maintenance treatment (after transplant or non-transplant therapy); and for strategies to manage lenalidomide-related toxicities.

Methods

Outcomes of interest included overall survival, event-free survival, progression-free survival, time to progression, time to next treatment, response rate, and incidence of serious toxicity. The MEDLINE, EMBASE, and Cochrane Library databases, as well as meeting abstracts and the Web sites of relevant organizations, were systematically searched for relevant literature.

Results

Recommendations were developed using the evidence from published studies and the clinical expertise of the working group and of the Cancer Care Ontario Hematology Disease Site Group.

Conclusions

Lenalidomide in combination with dexamethasone can be recommended for both previously untreated and treated patients with multiple myeloma. Guidelines for the management of cytopenias, venous thromboembolism, and second primary malignancies are discussed.

KEY WORDS

Lenalidomide, multiple myeloma, IMiD, practice guideline

1. INTRODUCTION

Lenalidomide was first approved for use in multiple myeloma patients who had received at least 1 prior therapy, based on results from two large randomized trials comparing lenalidomide plus dexamethasone with placebo plus dexamethasone^{1,2}. Since then, the role of lenalidomide has been investigated in expanded roles and novel combinations. Toxicities such as cytopenias, venous thromboembolism (VTE), and the potential risk of second primary malignancies (SPMS) pose challenges in the management of patients receiving lenalidomide.

The Cancer Care Ontario (CCO) Hematology Disease Site Group (DSG), in collaboration with the Program in Evidence-Based Care (PEBC) developed recommendations for the use of lenalidomide in multiple myeloma as part of a trilogy of guidelines for the treatment of myeloma using three novel backbone agents: thalidomide, bortezomib, and lenalidomide. The recommendations presented here provide practical, evidence-based guidance concerning indications for use, dosing, combinations under investigation, and management of key toxicities.

2. METHODS

This practice guideline was developed by the Hematology DSG of CCO's PEBC using the methods of the practice guidelines development cycle³. The PEBC is editorially independent of CCO and the Ontario Ministry of Health and Long-Term Care.

2.1 Questions

- Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with

previously untreated multiple myeloma (including smoldering and symptomatic patients, and candidates or non-candidates for transplant) compared with non-lenalidomide-containing treatments?

- Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with relapsed or refractory multiple myeloma compared with non-lenalidomide-containing treatments?
- Which multiple myeloma patients, both previously untreated and relapsed or refractory, are more or less likely to benefit from treatment with lenalidomide?
- Are outcomes in myeloma patients improved with the use of lenalidomide as maintenance or consolidation treatment (after transplant and non-transplant treatments) compared with either non-lenalidomide-containing treatment or no maintenance or consolidation treatment?
- What are the best strategies to manage lenalidomide-induced toxicity?

2.2 Target Population

The target population for this guideline is adult patients with previously untreated, relapsed, or refractory multiple myeloma.

2.3 Systematic Review

The literature was systematically searched using electronic databases (MEDLINE, EMBASE, and the Cochrane Library; meeting proceedings of the American Society of Hematology, the American Society of Clinical Oncology, and the International Myeloma Workshops), relevant Web sites such as CancerGuidelines.ca, the U.S. National Guideline Clearinghouse, the Canadian Medical Association Infobase, the Physician Data Query database, and the American College of Physicians Journal Club; and reference lists of included articles.

2.4 Study Selection Criteria

Articles published from January 2000 to February 2012, inclusive, were selected for this systematic review if they were

- studies of adult patients with multiple myeloma.
- studies that tested the role of lenalidomide alone or in combination with other agents.
- studies that reported results for any of the following outcomes:
 - overall survival (OS)
 - event-free survival
 - progression-free survival (PFS)
 - time to progression (TTP)
 - time to next treatment
 - response rate (complete and partial)
 - incidence of serious toxicity (that is, grade 3 or 4 adverse events by the National Cancer Institute toxicity criteria)

- studies that were systematic reviews or randomized controlled trials (RCTs: phase II or phase III).
- nonrandomized studies that were follow-ups or subanalyses of previous pivotal studies.
- studies with a trial sample size of 30 or more.
- studies published in English.

Narrative reviews, phase I trials, observational studies, case reports, noncomparative studies, and publication types such as commentaries, editorials, and letters were excluded. Conference abstracts that were reports of non-final analyses were also excluded. Cost-effectiveness and health-related quality of life were not outcomes of interest for this document.

2.5 Selection of Studies

Citations located in the search were screened independently by the methodologist and by two clinician members of the Working Group.

2.6 Development of Recommendations

The Hematology DSG developed draft recommendations based both on consensus and on evidence from the systematic review.

2.7 Internal and External Review

Before submission of the draft report for external review, the systematic review and practice guideline were reviewed by the PEBC Report Approval Panel. The draft report was distributed to health care providers in the province of Ontario for feedback, the results of which can be found in the full guideline report on the cco Web site: <https://www.cancercare.on.ca/toolbox/qualityguidelines/>.

3. RESULTS AND RECOMMENDATIONS

3.1 Literature Search Results

The search identified 9209 citations (Figure 1). After full text screening, fifty-two publications were included: two practice guidelines^{4,5}; three systematic reviews^{6–8}; ten unique primary studies, of which five were full-text publications^{1,2,9–11} and five were conference abstracts^{12–16}. Forty-two publications were ancillary to the ten unique primary studies, including secondary analyses or follow-up data from the main publications (Table 1).

A search for ongoing trials at ClinicalTrials.gov, performed April 2, 2012, identified 134 trials involving lenalidomide and multiple myeloma. Of those trials, thirty-four were RCTs, either phase II or phase III. Details of the included trials can be found in the full guideline report at the cco Web site (<https://www.cancercare.on.ca/toolbox/qualityguidelines/>).

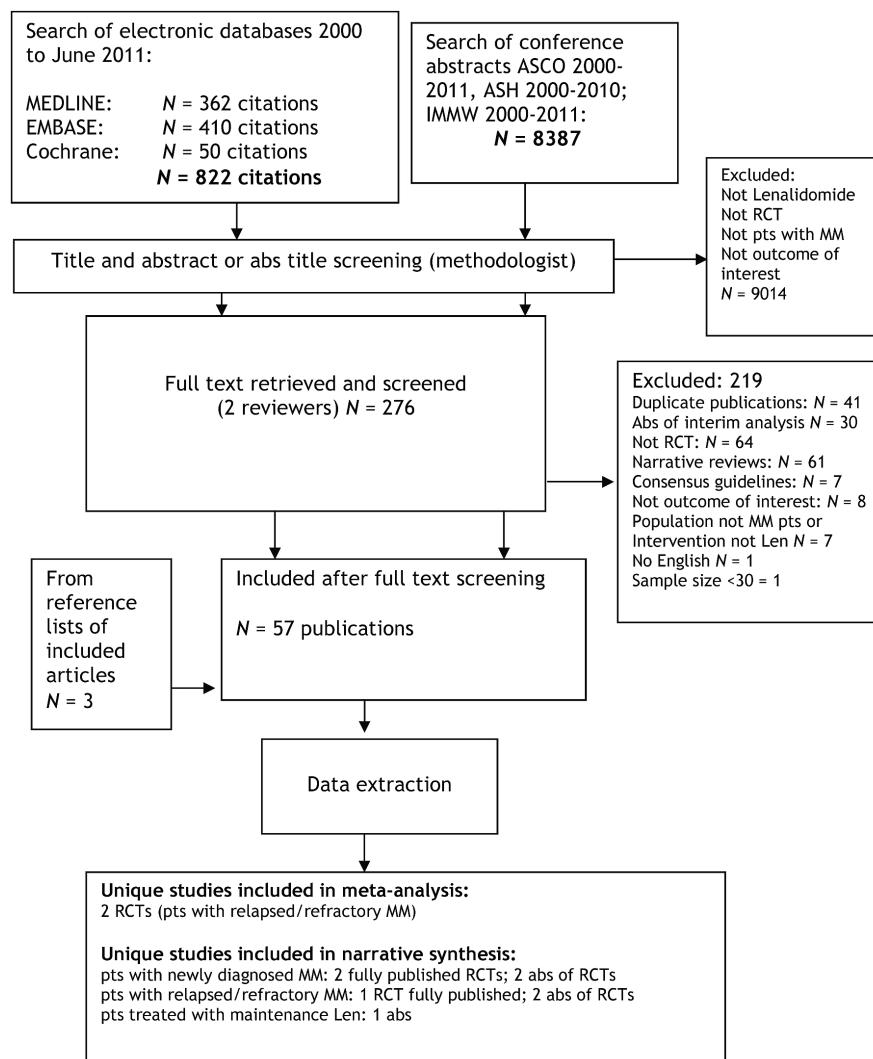


FIGURE 1 Study flow chart.

3.2 Question 1—Previously Untreated Patients

Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with previously untreated multiple myeloma (including smoldering and symptomatic patients, and candidates or non-candidates for transplant) compared with non-lenalidomide-containing treatments?

3.2.1 Recommendations

Previously Untreated Smoldering Multiple Myeloma: In asymptomatic patients with no evidence of myeloma-related hypercalcemia, renal dysfunction, anemia, or bone disease (smoldering myeloma), the use of lenalidomide alone or in combination cannot be recommended.

Previously Untreated Symptomatic Multiple Myeloma: Single-Agent Lenalidomide: Lenalidomide

alone cannot be recommended for standard use in this setting.

Lenalidomide and Dexamethasone: The combination of lenalidomide and dexamethasone is an acceptable first-line treatment option for myeloma. Recommended dosing options for lenalidomide include either giving 25 mg daily on days 1–28 every 35-day cycle for the first 3 cycles, followed by 25 mg daily on days 1–21 every 28-day cycle thereafter; or proceeding directly to the 28-day cycle dosing at onset. The use of low-dose dexamethasone—40 mg daily on days 1, 8, 15, and 22 of a 28-day cycle—is preferred for safety; however, select patients with acute myeloma complications such as renal dysfunction, hypercalcemia, or hyperviscosity may benefit from high-dose dexamethasone (that is, 40 mg daily on days 1–4, 9–12, and 17–20 of a 28-day cycle).

Other Lenalidomide Combinations: No other combinations can be recommended.

3.2.2 Key Evidence

Previously Untreated Smoldering Multiple Myeloma: In asymptomatic smoldering myeloma, an ongoing randomized trial that is evaluating lenalidomide in combination with dexamethasone, compared with the conventional watch-and-wait approach until symptomatic disease progression, is showing promising preliminary results favouring the use of early lenalidomide⁵⁹. However, no recommendations can be made for this population until the data have matured.

Previously Untreated Symptomatic Multiple Myeloma: No RCTs comparing lenalidomide alone with a non-lenalidomide regimen for first-line therapy both in candidates and in non-candidates for transplant were located.

The study by Zonder *et al.*⁹ showed an improved median 1-year PFS (78% vs. 52%, $p = 0.002$) and improved OS (77% vs. 48%, $p < 0.0001$) in patients receiving lenalidomide plus dexamethasone compared with placebo plus dexamethasone. Rajkumar *et al.*¹⁰ demonstrated a longer median PFS for lenalidomide plus low-dose dexamethasone than for lenalidomide plus high-dose dexamethasone (25.3 months vs. 19.1 months, $p = 0.026$), with an improved safety profile (grade 3 or greater adverse events: $p = 0.02$ for neutropenia, $p = 0.0003$ for DVT, and $p = 0.04$ for infections) in favour of the low-dose dexamethasone arm.

No RCTs of lenalidomide in combination with other agents in this setting were identified.

3.2.3 Qualifying Statements

The Zonder and Rajkumar studies^{9,10} have limitations: Both studies were stopped early because of observed benefit, and the Rajkumar study used overall response rate as a primary outcome. In the Rajkumar study, the improved safety profile and lower rate of early deaths with low-dose dexamethasone has led to widespread adoption of that approach. From a safety perspective, the Hematology DSG endorses it. It should be noted, however, that compared with low-dose dexamethasone, high-dose dexamethasone, although more toxic, was associated with higher response rates. Therefore, in select patient populations with acute myeloma-related complications, benefit might still be obtained from the robust efficacy of high-dose dexamethasone.

3.3 Question 2—Patients with Relapsed or Refractory Multiple Myeloma

Does lenalidomide (alone or in combination with other therapies) improve outcomes in patients with

relapsed or refractory multiple myeloma compared with non-lenalidomide-containing treatments?

3.3.1 Recommendations

Single-Agent Lenalidomide: Lenalidomide alone cannot be recommended for standard use in the relapsed or refractory setting.

Lenalidomide and Dexamethasone: The combination of lenalidomide and dexamethasone is recommended for myeloma patients who have received at least 1 prior line of therapy. The recommended dosing is lenalidomide 25 mg daily on days 1–21, plus dexamethasone (either low-dose 40 mg daily on days 1,8,15, and 22, or high-dose 40 mg daily on days 1–4, 9–12, and 17–20) in a 28-day cycle.

Other Lenalidomide Combinations: No other combinations can be recommended.

3.3.2 Key Evidence

No randomized trials that compared lenalidomide as a single agent with a non-lenalidomide regimen in previously treated patients were located.

Two seminal studies^{1,2} showed an improved TTP for lenalidomide plus dexamethasone compared with dexamethasone plus placebo. Our meta-analysis of those two studies showed that, compared with a non-lenalidomide regimen, lenalidomide improved TTP [hazard ratio (HR): 0.35; 95% confidence interval (CI): 0.29 to 0.42; $p < 0.00001$], OS (HR: 0.54; 95% CI: 0.36 to 0.80; $p < 0.002$), and overall response (HR: 0.50; 95% CI: 0.44 to 0.58; $p < 0.00001$).

Although high-dose dexamethasone in combination with lenalidomide was used in the two pivotal RCTs of relapsed or refractory myeloma, low-dose weekly dexamethasone with lenalidomide appears less toxic when used in the first line¹⁰. From a safety perspective, the Hematology DSG considers low-dose dexamethasone a reasonable option for the relapsed or refractory setting. Again, select subgroups with acute myeloma complications may benefit from the greater response rates achievable with high-dose dexamethasone.

No RCTs of lenalidomide in combination with other agents in this setting were identified.

3.3.3 Qualifying Statements

Both of the seminal studies^{1,2} were stopped at the first preplanned interim analysis for benefit and were funded by the drug's manufacturer. However, the studies enrolled more than 300 patients before stopping and had a large number of events.

The recommendation to use low-dose dexamethasone with lenalidomide in the relapsed or refractory setting is generalized from the first-line Rajkumar study¹⁰ and is based primarily on improved safety. No comparative studies have evaluated low-dose dexamethasone dosing in the relapsed or refractory setting.

TABLE 1 Lenalidomide (LEN) in multiple myeloma (MM): primary and ancillary publications of identified randomized trials and their objectives

<i>Study name</i>	<i>Primary publication</i>	<i>Investigation</i>	<i>Additional publications</i>	<i>Investigation</i>
MM-009	Weber <i>et al.</i> , 2007 ¹	Compare LEN plus dexamethasone (DEX) with placebo (PLC) plus DEX in relapsed or refractory MM	Zangari <i>et al.</i> , 2010 ¹⁷ Dimopoulos <i>et al.</i> , 2010 ¹⁸ Harousseau <i>et al.</i> , 2010 ¹⁹ Castaneda <i>et al.</i> , 2010 (abstract) ²⁰ Baz <i>et al.</i> , 2010 (abstract) ²¹	Pooled subgroup analysis investigating the effect of thromboembolic complications Pooled subgroup analysis of patients with impaired renal function Pooled subgroup analysis of patients with complete or very good partial response and those with partial response Pooled subgroup analysis for the evaluation of peripheral neuropathy and adverse events Pooled subgroup analysis for the evaluation of the occurrence of viral infections
MM-010	Dimopoulos <i>et al.</i> , 2007 ²	Compare LEN plus DEX with PLC plus DEX in relapsed or refractory MM	Baz <i>et al.</i> , 2009 (abstract) ²² Lonial <i>et al.</i> , 2009 (abstract) ²³ Delforge <i>et al.</i> , 2009 (abstract) ²⁴ Dimopoulos <i>et al.</i> , 2009 (abstract) ²⁵ Dimopoulos <i>et al.</i> , 2006 (abstract) ²⁶ Dimopoulos <i>et al.</i> , 2009 ²⁷ Wang <i>et al.</i> , 2008 ²⁸ Hazarika <i>et al.</i> , 2008 ²⁹ San Miguel <i>et al.</i> , 2011 ³⁰	Pooled subgroup analysis investigating the effect of LEN plus DEX on levels of immunoglobulin A (IgA) Pooled subgroup analysis investigating the incidence, onset, and duration of neutropenia Pooled subgroup analysis of patients with and without a history of peripheral neuropathy Pooled subgroup analysis of LEN dose adjustments to determine an optimal long-term treatment strategy Pooled subgroup analysis investigating the effect of number of prior therapies Long-term follow-up of the two pivotal randomized trials Pooled subgroup analysis examining prior thalidomide exposure Regulatory perspectives; same data as original studies Pooled subgroup analysis investigating the effect on survival of continuing therapy after achievement of a partial response or better

TABLE 1 Continued

<i>Study name</i>	<i>Primary publication</i>	<i>Investigation</i>	<i>Additional publications</i>	<i>Investigation</i>
			Simpson <i>et al.</i> , 2008 (abstract) ³¹	Pooled subgroup analysis evaluating the frequency of diarrhea in newly diagnosed patients from two studies conducted at the Mayo Clinic and relapsed or refractory patients from the MM009 and MM010 trials
			Foa <i>et al.</i> , 2007 (abstract) ³²	Pooled subgroup analysis of IgA subtype of myeloma
			San Miguel <i>et al.</i> , 2007 (abstract) ³³	Pooled subgroup analysis of the effect of DEX dose reductions
			Lonial <i>et al.</i> , 2007 (abstract) ³⁴	Pooled subgroup analysis of age categories
			Chanan-Khan <i>et al.</i> , 2006 (abstract) ³⁵	Pooled subgroup analysis of age categories
			Chanan-Khan <i>et al.</i> , 2006 (abstract) ³⁶	Pooled subgroup analysis of prior autologous stem-cell transplantation (ASCT)
			Chanan-Khan <i>et al.</i> , 2007 (abstract) ³⁷	Pooled subgroup analysis of the effect of performance status
			Niesvizky <i>et al.</i> , 2006 (abstract) ³⁸	Pooled subgroup analysis of the effect of thrombosis
			Stadtmauer <i>et al.</i> , 2009 ³⁹	Pooled subgroup analysis of LEN at first relapse compared with later salvage
			Richardson <i>et al.</i> , 2011 (abstract) ⁴⁰	Examination of the risk of secondary malignancies
			Dimopoulos <i>et al.</i> , 2011 ⁴¹	Examination of the risk of secondary primary malignancies
			Dimopoulos <i>et al.</i> , 2011 ⁴²	Pooled subgroup analysis of patients who had not progressed and were still receiving LEN at 12 months
			Dimopoulos <i>et al.</i> , 2011 (abstract) ⁴³	Pooled subgroup analysis at 48 months' follow-up of patients with progression-free survival of 2 years or better
S0232	Zonder <i>et al.</i> , 2010 ⁹	Compare LEN plus DEX with PLC plus DEX as first-line treatment for MM	Zonder <i>et al.</i> , 2008 (abstract) ⁴⁴	Partial results of study and subgroup analysis of abnormal karyotype and high-risk cytogenetic abnormalities
			Zonder <i>et al.</i> , 2011 (abstract) ⁴⁵	Extended results

TABLE 1 Continued

Study name	Primary publication	Investigation	Additional publications	Investigation
E4A03	Rajkumar <i>et al.</i> , 2010 ¹⁰	Whether low-dose DEX plus LEN is noninferior to and has lower toxicity than high-dose DEX plus LEN in newly diagnosed MM	Siegel <i>et al.</i> , 2010 (abstract) ⁴⁶ Jacobus <i>et al.</i> , 2010 (abstract) ⁴⁷ Jacobus <i>et al.</i> , 2011 ⁴⁸ Vesole <i>et al.</i> , 2010 ⁴⁹ Harvey <i>et al.</i> , 2011 (abstract) ⁵⁰	Subgroup analysis based on age group and subsequent ASCT Subgroup analysis of patients 70 years of age or older Subgroup analysis of patients with a FISH-based genetic classification Subgroup analysis of older patients Evaluate the impact of renal function on LEN dosing, cytopenias, and response
	Richardson <i>et al.</i> , 2006 ¹¹	Evaluate 2 dose regimens of LEN for relapsed or refractory MM		
RV-MM-PI-209	Palumbo <i>et al.</i> , 2011 (abstract) ¹⁵	To compare LEN plus melphalan (MEL) plus prednisone with tandem MEL [200 mg/m ² (MEL200)] in newly diagnosed MM patients who received LEN during induction; 14 months' follow-up data	Larocca <i>et al.</i> , 2011 ⁵¹	Efficacy and safety of low-molecular weight heparin compared with ASA as thromboprophylaxis in newly diagnosed patients less than 65 years of age, treated with LEN-based regimens
			Palumbo <i>et al.</i> , 2011 (abstract) ⁵²	Results at 20 months' follow-up
			Palumbo <i>et al.</i> , 2011 (abstract) ⁵³	Results at 26 months' follow-up
IFM 2005-02	Attal <i>et al.</i> , 2011 (abstract) ¹⁴	To investigate the efficacy of LEN for maintenance after transplantation	Attal <i>et al.</i> , 2011 (abstract) ⁵⁴ Attal <i>et al.</i> , 2010 (abstract) ⁵⁵	Presents additional data Presents additional data
	Zangari <i>et al.</i> , 2003 (abstract) ¹⁶	Compare two doses of LEN in relapsed or refractory disease	=	=
EVOLUTION	Kumar <i>et al.</i> , 2011 (abstract) ¹³	To compare various combinations of bortezomib, DEX, cyclophosphamide, and LEN in previously untreated MM	Kumar <i>et al.</i> , 2009 (abstract) ⁵⁶	Reports noncomparative data
	Richardson <i>et al.</i> , 2011 (abstract) ¹²	To evaluate the efficacy of elotuzumab plus LEN and low-dose DEX in relapsed refractory MM	Lonial <i>et al.</i> , 2011 (abstract) ⁵⁷	Updated results (73 patients)

TABLE 1 Continued

Study name	Primary publication	Investigation	Additional publications	Investigation
<i>Systematic reviews</i>				
Carrier (thrombo-prophylaxis)	Carrier <i>et al.</i> , 2011 ⁸	To determine the absolute rates of venous thromboembolism with and without various thromboprophylactic agents (ASA, warfarin, low-molecular weight heparin) in newly diagnosed or previously treated MM patients receiving thalidomide- or LEN-based regimens	Not applicable	
Richardson (use of LEN)	Richardson <i>et al.</i> , 2010 ⁶	To evaluate the evidence for the use of LEN in its current indication in relapsed or refractory MM, and additionally its investigational use for the treatment of newly diagnosed MM	Not applicable	
Boen (venous thrombo-embolism)	Boen <i>et al.</i> , 2008 (abstract) ⁷	To compare the LEN/thalidomide/DEX-associated venous thromboembolism rates pre- and post-FDA approval	Not applicable	
<i>Practice guidelines</i>				
ASCO guideline (treatment of venous thrombo-embolism in cancer patients)	Lyman <i>et al.</i> , 2007 ⁴	Recommendation for patients treated with LEN (p. 5501)	Not applicable	
NICE guideline	NICE, 2009 ⁵	Recommendations for the use of LEN in patients who have received at least 1 prior line of treatment	Hoyle <i>et al.</i> , 2008 ⁵⁸	Technology assessment

FISH = fluorescence *in situ* hybridization; ASA = acetylsalicylic acid; FDA = U.S. Food and Drug Administration; ASCO = American Society of Clinical Oncology; NICE = U.K. National Institute for Health and Clinical Excellence.

3.4 Question 3—Subgroups Most Likely to Benefit

Which multiple myeloma patients, both previously untreated and relapsed or refractory, are more or less likely to benefit from treatment with lenalidomide?

3.4.1 Recommendations

For patients with untreated myeloma, the evidence is insufficient to recommend lenalidomide in specific patient subgroups. When lenalidomide is combined with dexamethasone, the use of low-dose rather than high-dose dexamethasone may be preferable from a safety perspective, regardless of age.

For patients with relapsed or refractory multiple myeloma, lenalidomide plus dexamethasone is reasonable for the following patient subgroups:

- Patients who have received at least 1 prior line of therapy. Patients who are less heavily treated

(only 1 prior line of therapy vs. 2 or more) appear to benefit the most.

- Patients who have received prior thalidomide or stem-cell transplantation.
- Younger or older patients. Advanced age should not be an absolute contraindication to the use of lenalidomide. Careful monitoring for toxicities is recommended.
- Patients with mild-to-moderate renal failure (creatinine clearance ≥ 30 mL/min and ≤ 60 mL/min). For patients with severe renal failure (creatinine clearance < 30 mL/min), the Hematology DSG cautions about the use of lenalidomide until additional evidence for its use in this subgroup becomes available.
- Patients with immunoglobulin A subtype, pre-existing peripheral neuropathy, and varying levels of Eastern Cooperative Oncology Group performance status.

For patients with relapsed or refractory multiple myeloma, the following treatment guidelines for lenalidomide and dexamethasone may be considered:

- Full-dose lenalidomide may be initiated (25 mg daily), but it is reasonable to consider dose reductions for use beyond 12 months.
- A longer period of lenalidomide use, if possible until progression, is a reasonable target.
- Dexamethasone dose reductions may be used as needed for improved tolerability.

3.4.2 Key Evidence

The subgroup analyses of data are derived primarily from the Rajkumar study¹⁰ in the first-line setting and from pooled data from the Weber and Dimopoulos studies^{1,2,10,18,34,35,39} in the relapsed or refractory setting. These data have been integrated with the clinical expertise of the Hematology DSG to provide support for the recommendations.

Evidence to recommend lenalidomide in specific subgroups of previously untreated patients is limited. When lenalidomide is combined with dexamethasone, the use of low-dose dexamethasone may be preferable in older and younger patients alike. Two subgroup analyses based on the age of patients participating in the Rajkumar study¹⁰ reported improved OS in all age groups when treated with low-dose rather than high-dose dexamethasone^{47,49}.

- The recommendation for lenalidomide plus dexamethasone in patients who have received at least 1 prior line of therapy derives from study stratification results and a pooled subgroup analysis by Stadtmauer *et al.*³⁹ from the Weber and Dimopoulos studies^{1,2}.
- The subgroup analysis by Wang *et al.*²⁸ showed that there may be partial cross-resistance between thalidomide and lenalidomide, but that prior thalidomide exposure should not absolutely contraindicate the use of lenalidomide in the relapsed or refractory setting. The recommendation for patients who have undergone prior autologous stem-cell transplantation is based on study stratification results and a pooled subgroup analysis by Dimopoulos *et al.*²⁶.
- The recommendation for use of lenalidomide in older as well as younger patients is based on a subgroup analysis of the Weber and Dimopoulos studies^{1,2} reported by Chanan-Khan *et al.*³⁵.
- Lenalidomide is excreted primarily by the kidneys, posing a risk for cumulative drug-related toxicity with renal dysfunction. The recommendation for use in mild-to-moderate renal dysfunction (creatinine clearance ≥ 30 mL/min and ≤ 60 mL/min) is based on a subgroup analysis of pooled data from the pivotal relapsed or refractory studies^{1,2} reported by Dimopoulos *et al.*¹⁸ Given the small sample of patients with severe

renal failure (creatinine clearance < 30 mL/min) enrolled in the studies, the Hematology DSG cannot make recommendations for that population.

- Lenalidomide and dexamethasone were found to be consistently superior to dexamethasone alone in several subgroup analyses^{24,32,37}.
- The guideline on dose reduction is supported by the Dimopoulos *et al.* subgroup analysis of patients remaining on lenalidomide beyond 12 months²⁵. Those authors report that patients requiring dose reductions were able to stay on study longer, tolerated therapy as well as those not requiring dose reductions, and achieved a longer PFS.
- The guideline suggesting continuing treatment until progression, if feasible, is based on two subgroup analyses by San Miguel *et al.*³⁰ and Harousseau *et al.*¹⁹ suggesting that continued therapy after achievement of a partial response is beneficial, possibly by improving quality of response, which in turn prolongs survival.
- The guideline on dexamethasone reduction for tolerability is based on a subgroup analysis by San Miguel *et al.*³³ that associated dose reductions of dexamethasone with improved survival outcomes.

3.4.3 Qualifying Statements

All subgroup analyses upon which the recommendations are based are retrospective *post hoc* analyses. In isolation, they represent a weak evidence base and therefore have been integrated with the expert opinion and clinical experience of the Hematology DSG. Validation of these recommendations through further clinical investigation is required.

3.5 Question 4—Maintenance or Consolidation Treatment

Are outcomes in myeloma patients improved with the use of lenalidomide as maintenance or consolidation treatment (after transplant and non-transplant treatments) compared with either non-lenalidomide-containing treatment or no maintenance or consolidation treatment?

3.5.1 Recommendations

Non-Candidates for Transplant: The evidence is insufficient to support the use of lenalidomide maintenance or consolidation treatment after initial non-transplant therapy.

Candidates for Transplant: In the absence of a final full publication of supporting trials in the post-transplant setting (currently published as conference abstracts^{14,54,55,60}), the Hematology DSG recommends that lenalidomide maintenance at 10–15 mg daily continuously until progression is a reasonable option.

3.5.2 Key Evidence

In non-candidates for transplant, a randomized trial reported by Palumbo *et al.*⁶¹ evaluating lenalidomide as maintenance after melphalan, prednisone, and lenalidomide therapy showed promising preliminary results, but did not provide adequate mature evidence to support a recommendation for use.

In three companion abstract publications^{14,54,55}, a significant improvement in PFS ($p < 0.0001$) was reported with maintenance compared with no maintenance after transplant. In addition, an ongoing randomized study, presented in preliminary form, strongly supported the benefit of post-transplant maintenance, with an OS advantage. The median TTP was 43.6 months compared with 21.5 months, and PFS was also favourable for the lenalidomide group (HR: 0.43; one-sided unadjusted $p < 0.0001$)⁶⁰. These combined data provide emerging support for the use of lenalidomide maintenance post transplant, which the Hematology DSG considers a reasonable post-transplant option.

3.5.3 Qualifying Statements

The Palumbo⁶², Attal⁶³, and McCarthy⁶⁴ maintenance trials were recently published in full, but were not captured within our search cut-off dates. Therefore all recommendations in the present guidelines are based on ongoing trial data available at the time of the literature search. Data from the study by Attal *et al.*^{14,54,55} is based on a final analysis of the completed data, but presented in abstract form. That study was stopped early for benefit. Data from the study by McCarthy *et al.*⁶⁰ is based on an interim analysis that had already shown OS benefit. Although the abstract data are adequately compelling for the Hematology DSG to recommend maintenance in post-transplant patients, evaluation of the full publications with further maturation is required before full recommendations can be made.

3.6 Question 5—Management of Toxicity

What are the best strategies to manage lenalidomide-induced toxicity?

3.6.1 Recommendations

VTE: For newly diagnosed patients, and for relapsed or refractory patients who are not at high risk for bleeding or VTE, either daily low-dose acetylsalicylic acid (ASA) 100 mg given orally or daily enoxaparin (low molecular weight heparin) 40 mg given subcutaneously can be used in patients treated with lenalidomide-based therapy to prevent VTE. For patients at high risk of VTE or bleeding, the evidence is insufficient to support a specific thromboprophylactic approach. If ASA in a 100 mg dose form is not available, the Hematology DSG suggests that replacement with the 81 mg dose form is reasonable.

Cytopenias: The evidence is insufficient to recommend a uniform approach for the management of cytopenias. Lenalidomide dose reductions can be considered for patients who have responded to full-dose lenalidomide. For those who require the full dose of lenalidomide for efficacy, the use of granulocyte colony-stimulating factor can be considered for neutropenia support.

For the management of anemia and thrombocytopenia, there are no randomized data evaluating approaches in the lenalidomide setting, including the use of erythropoiesis-stimulating agents (ESAs).

SPMs: The evidence to date is insufficient to confirm or refute the association of SPM with lenalidomide or to identify specific subgroups of patients at risk of SPM when treated with lenalidomide.

3.6.2 Key Evidence

The recommendation on VTE is based on a published substudy of patients participating in a lenalidomide-based study for first-line use, randomized to either oral ASA 100 mg daily or subcutaneous enoxaparin 40 mg daily for VTE prophylaxis⁵¹. Equally low rates of VTE, with no major hemorrhagic complications were reported for both trial arms, and therefore the Hematology DSG recommends either option as reasonable. Given the favourable safety profile of both ASA and enoxaparin in prophylactic dosing, generalization of the recommendation to the relapsed or refractory setting is not unreasonable until randomized data in that setting become available. Patients at high risk for VTE (prior deep vein thrombosis in the preceding 12 months) or bleeding were not enrolled in the supporting study; the recommendation therefore cannot be extended to that subgroup.

The cytopenia recommendation for lenalidomide dose reductions was based on a subgroup analysis of data pooled from the Weber and Dimopoulos trials^{1,2,25} suggesting that dose reductions might allow patients to tolerate therapy longer, leading to prolonged PFS. However, in the pivotal RCTs, routine use of granulocyte colony-stimulating factor with full-dose lenalidomide was mandated as initial management for severe neutropenia^{1,2}. Based on those data and the clinical expertise of the Hematology DSG, the recommended options include either dose reductions in patients with responsive disease or granulocyte colony-stimulating factor support if full-dose lenalidomide is required for efficacy.

3.6.3 Qualifying Statements

The Larocca *et al.* superiority trial⁵¹ showed no difference between two drugs for the prevention of VTE; untreated patients were 65 years of age or younger, the power of the study ranged from 47% to 80%, and for ethical reasons, a placebo arm was not used. However, this trial was the only RCT to study

VTE prophylaxis in patients with myeloma treated with lenalidomide. Despite the study limitations, the Hematology DSG felt that, based on clinical experience, the results could be generalized to other patient groups.

In the absence of evidence for ESA use specific to lenalidomide, the Hematology DSG suggests that published evidence-based guidelines for ESA use in cancer may be applied^{65,66}. In a subgroup analysis of the Weber and Dimopoulos studies published as a letter to the editor and excluded from our systematic review, the rates of VTE were significantly higher with concomitant use of ESA and lenalidomide than with lenalidomide without ESA⁶⁷. Because these observations mandate further validation, the Hematology DSG advises consideration of risks and benefits before initiating ESA with lenalidomide, followed by careful monitoring for VTE.

4. CONCLUSIONS

Lenalidomide is an active agent for the treatment of multiple myeloma. There is sufficient evidence to recommend lenalidomide for myeloma patients who are previously untreated, who have received at least 1 prior line of therapy, and who are post-transplant, for maintenance. Data to provide guidance for patient selection, dosing, and management of toxicities are increasing. There is, however, an ongoing need for studies comparing lenalidomide-based regimens with regimens utilizing other novel agents such as bortezomib, and studies evaluating rational lenalidomide combinations, novel roles such as consolidation or maintenance, strategies for the management of toxicities, and the long-term risks with lenalidomide. In this rapidly evolving field, vigilant scrutiny of the literature on an ongoing basis is required.

5. REVIEW AND UPDATE

Practice guidelines developed by the PEBC are reviewed and updated regularly. Please visit the CCO Web site (<http://www.cancercare.on.ca>) for the full evidence-based series report (<https://www.cancercare.on.ca/toolbox/qualityguidelines/>) and subsequent updates.

6. ACKNOWLEDGMENTS

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7. CONFLICT OF INTEREST DISCLOSURES

Among the authors of this report, CC has received research support from Celgene, and MC is a site investigator on trial MM020, sponsored by Celgene. Among the members of the DSG, Dr. Donna Reece has received trial support from Celgene, BMS, Janssen, Johnson & Johnson, Otsuka, Novartis, and Merck; Dr. Ralph Meyer has received research funding from Celgene and is an independent research assessment committee member in a Celgene-sponsored trial, receiving an annual honorarium of less than \$5000; Dr. Andre Schuh is a principal investigator on a clinical trial of lenalidomide; Dr. Tom Kouroukis is a member of the Celgene Canadian Advisory Board and a local principal investigator in the FIRST study, sponsored by Celgene. All the other members of the Working Group and of the DSG declared no conflict of interest.

All members of the Report Approval Panel declared no conflict of interest.

Among the four external reviewers constituting the technical expert panel, Dr. Vishal Kukreti declared honoraria for acting as a consultant to Celgene, Roche, and Janssen-Ortho that exceeded \$5,000 in one year. Dr. Kukreti also declared principal investigator status in a phase III lenalidomide trial. All the other member of the panel declared no conflict of interest.

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