Better quality of response to lenalidomide plus dexamethasone is associated with improved clinical outcomes in patients with relapsed or refractory multiple myeloma

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ABSTRACT

Background
This retrospective pooled analysis of two phase III trials (MM-009/MM-010) compared clinical outcomes of patients who achieved a complete response or very good partial response to treatment with lenalidomide plus dexamethasone with the outcomes of those who only achieved a partial response.

Design and Methods
Patients (n=353) received lenalidomide (25 mg/day for 21 days of each 28-day cycle) plus dexamethasone (40 mg on days 1–4, 9–12, and 17–20 for four cycles, and only on days 1–4 after the first four cycles). Time to response, duration of response, time-to-progression, overall survival, and adverse events were investigated for patients who had a complete or very good partial response and compared with those of patients who had a partial response.

Results
At the time of unblinding, 32% of patients had achieved a complete or very good partial response and 28% had a partial response. Half (50.5%) of the patients who had a partial response as their initial response achieved a complete or very good partial response with further treatment. The probability of achieving a complete or very good partial response with continued lenalidomide treatment decreased with delayed achievement of a partial response (by cycle 4 *versus* later); however, it remained clinically significant. With an extended follow-up of 48 months, the median response duration, time-to-progression, and overall survival were longer in patients with a complete or very good partial response than in those with a partial response (24.0 *versus* 8.3 months, $P<0.001$; 27.7 *versus* 12.0 months, $P<0.001$; not reached *versus* 44.2 months, $P=0.021$, respectively). The benefit of a complete or very good partial response was independent of when it was achieved.

Conclusions
Continuing treatment with lenalidomide plus dexamethasone to achieve best response, in the absence of disease progression and toxicity, provided deeper remissions and greater clinical benefit over time for patients in this study.

Key words: lenalidomide, dexamethasone, multiple myeloma, response, clinical benefit, efficacy.

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Introduction

Patients with newly diagnosed multiple myeloma who achieve a complete response (CR) or a very good partial response (VGPR) to high-dose chemotherapy and autologous stem cell transplantation are more likely to have a favorable long-term survival than those achieving less than a CR/VGPR.[1-4] The prognostic impact of the quality of response has been demonstrated primarily in newly diagnosed patients with multiple myeloma treated with high-dose therapy, whereas there is less information regarding patients with relapsed or refractory disease. The major reason for the scarcity of such data in patients with relapsed or refractory disease is the small number of patients who achieved CR/VGPR in historical studies, leading to a lack of power in demonstrating significant differences. With the availability of new therapeutic options, such as lenalidomide and bortezomib, higher response rates have been achieved allowing for assessment of the prognostic impact of response quality in relapsed or refractory multiple myeloma. Recently, the benefit of CR on response duration was demonstrated among patients treated with bortezomib.[5,6]

Lenalidomide (Revlimid®; Celgene Corporation, NJ, USA) is an oral immunomodulatory compound, which has demonstrated significant efficacy in the treatment of patients with relapsed or refractory multiple myeloma.[7,8] In two recent phase III trials (MM-009 and MM-010) in this population of patients, lenalidomide plus dexamethasone treatment led to an overall response rate (with overall response defined as a partial response [PR] or better) of more than 60% (61.0% in MM-009 and 60.2% in MM-010), a CR rate of approximately 15% (14.1% and 15.9%, respectively), a median time-to-progression of at least 11.1 months (11.1 months and 11.3 months, respectively), and a median overall survival of at least 29.6 months (29.6 months and not yet reached at study unblinding in MM-009 and MM-010, respectively).[9,10] In both studies overall response rate, CR rate, time-to-progression, and overall survival were significantly superior with lenalidomide plus dexamethasone compared with dexamethasone alone.[9,10] The long-term follow-up study of patients from these registration trials demonstrated a significant benefit in overall survival with lenalidomide plus dexamethasone (median overall survival of 38.0 *versus* 31.6 months with placebo plus dexamethasone, P=0.045).[11]

Recent studies have shown that the overall response rate and the quality of response achieved with lenalidomide treatments increased over time in patients with newly diagnosed multiple myeloma.[12,13]

As treatment with lenalidomide plus dexamethasone increases the number of patients with relapsed or refractory multiple myeloma who achieve a CR/VGPR, it is important to determine whether relapsed or refractory patients who achieve this high quality of response have a clinically measurable benefit in comparison with patients who achieve only a PR. A subanalysis of pooled data from the MM-009 and MM-010 trials was performed in order to evaluate the effects on outcomes in patients with relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone who achieved a CR or VGPR as best response compared with the outcomes in those who achieved a PR.

Design and Methods

Pooled data from 353 patients randomized to the lenalidomide plus dexamethasone arm of two large multicenter, double-blind, placebo-controlled studies (MM-009 and MM-010) were analyzed. The protocols of these two studies were described in detail in the primary publications.[9,10] When the predetermined O'Brien–Fleming boundary for the superiority of lenalidomide over placebo was crossed, the study was unblinded and patients were allowed to cross over to open-label administration of lenalidomide at disease progression, or at the discretion of the investigator. Response to treatment was assessed by the investigators and reviewed centrally.

For the purpose of this analysis, the European Group for Blood and Marrow Transplantation (EBMT) criteria, as protocol-specified for the MM-009 and MM-010 studies, were adapted with the inclusion of VGPR under the International Myeloma Working Group (IMWG) uniform response criteria.[9,10,14,15] According to these criteria, responses were defined as follows: CR: no M-protein detectable by immunofixation in the serum and urine, disappearance of any soft tissue plasmacytomas, and 5% or fewer plasma cells in the bone marrow; VGPR (which includes near-CR): M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein and urine M-protein level less than 100 mg/24 hours; PR: 50% or greater reduction of serum M-protein and reduction in 24-hour urinary M-protein by 90% or more or to less than 200 mg/24 hours. Patients who achieved a CR/VGPR as their best response were assigned to one group (the CR/VGPR group) and those with a PR as their best response were assigned to the other group. Differences in time to response, duration of response, time-to-progression, overall survival, and adverse events between patients who achieved CR/VGPR as their best response and those who achieved PR as their best response were investigated.

Selection of patients

Eligible patients were aged at least 18 years, had progressive multiple myeloma after one or more treatments, and measurable disease that was susceptible to dexamethasone. Patients were considered dexamethasone-resistant if there was evidence of disease progression during previous high-dose dexamethasone-containing therapy (total monthly dexamethasone dose >200 mg). Measurable disease was defined as a serum M-protein level of 500 mg/dL or more, or a urine Bence-Jones protein level of 200 mg/24 hours or more. Additional eligibility criteria included: an Eastern Cooperative Oncology Group performance status score of 2 or more; serum aspartate aminotransferase or alanine aminotransferase levels less than three times the upper limit of normal; serum bilirubin levels less than twice the upper limit of normal; serum creatinine levels of less than 2.5 mg/L; an absolute neutrophil count of more than 1,000 cells/mm^3; and platelet counts of more than 75,000/mm^3 for patients with less than 50% bone marrow plasma cells, and more than 30,000/mm^3 for patients with 50% or more bone marrow plasma cells. Women of childbearing potential were required to use contraception, have a negative pregnancy test, and agree to a monthly pregnancy test until 4 weeks after discontinuation of the study drug.

Treatments

During each 28-day cycle, patients received oral lenalidomide (25 mg/day for 21 days in each cycle) plus dexamethasone (40 mg on days 1–4, 9–12, and 17–20 for four cycles, and only on days 1–4 after the first four cycles). Patients were treated until disease progression or unmanageable toxicity. The dose of lenalidomide was to be modified if grade 3/4 adverse events occurred. Treatment

was withheld until adverse events were resolved, and treatment was restarted at the next lower dose. The dosage modifications were 15 mg/day (level 1), 10 mg/day (level 2), and 5 mg/day (level 3). For grade 3/4 neutropenia without other adverse events, the first dose-modification was 25 mg/day plus granulocyte colony-stimulating factor at a dose of 5 μg per kilogram of body weight. To manage dexamethasone-related adverse events, the dose of dexamethasone was modified to 40 mg/day for 4 days every 2 weeks (dose level –1) or every 4 weeks (dose level –2), or 20 mg/day for 4 days every 4 weeks (dose level –3) at the discretion of the investigator.

Assessments

Blood counts and physical examinations were performed on days 1 and 15 (and day 8 of cycle 1) during cycles 1–3, and on day 1 of each cycle thereafter. Serum and urine protein electrophoresis studies were performed on day 1 of each 28-day cycle and at the end of treatment. Initial response was defined as the first documented response that could be confirmed at the following assessment; an unconfirmed first response was not scored as an initial response. Response duration was defined as the time from the first documented response to the first documentation of progressive disease in the trial, or censored at the last assessment if no progressive disease was documented. Time-to-progression was measured from the date of randomization to the date of the first assessment showing progression. Progressive disease was defined by any of the following criteria: an absolute increase of more than 500 mg/dL in serum M-protein compared with nadir; an absolute increase in urine M-protein greater than 200 mg/24 hours; new or increased size of bone lesions or plasmacytomas; or development of hypercalcemia (serum calcium greater than 11.5 mg/dL) in addition to a change from immunofixation-negative CR to an immunofixation-positive state. Patients who died before evidence of disease progression were censored at the last evaluation for assessment of time-to-progression. Response duration, time-to-progression, and overall survival were assessed at the time of the updated analysis, with a median follow-up of 48 months for surviving patients. An additional landmark analysis was performed at 12 months of follow-up on patients who were progression-free and remained on-study. Adverse events were graded according to the National Cancer Institute Common Toxicity Criteria (version 2, 2007).

Statistical analyses

Differences between the two groups of responders (those with CR/VGPR as best response *versus* those with PR as best response) with regards to the patients' characteristics at baseline were tested with pooled t-tests for continuous variables (e.g. age and time since diagnosis), or with Fisher's exact test for categorical variables (e.g. sex). The medians for time-to-event variables involving censoring (response duration, time-to-progression and overall survival) are based on Kaplan-Meier estimates, and the differences in these variables between the two groups of responders are based on two-tailed unstratified log-rank tests of the curves. Statistical significance was evaluated at the 0.05 alpha level. Analyses were performed using Statistical Analysis System version 9.1 (SAS Institute, Inc., Cary, NC, USA). The analyses performed were not pre-specified in the protocol and no adjustment for multiplicity was made.

Results

Patients' characteristics

Data from the 353 patients who were randomized to receive oral lenalidomide plus dexamethasone were evaluated. Among the 353 patients treated with lenalidomide plus dexamethasone in these clinical trials, 114 (32.3%) achieved a CR/VGPR and 100 (28.3%) patients had a PR at the time of unblinding. Patients who only achieved a PR had a longer median time since diagnosis (3.6 years *versus* 2.8 years, P=0.024), had received more prior antimyeloma regimens and/or stem cell transplants (P=0.038), and more prior thalidomide (41% *versus* 24%, P=0.008) compared with those patients who achieved a CR/VGPR as best response (Table 1). The median duration of treatment was longer in patients who achieved CR/VGPR as best response than in those who had a PR (16.0 months, [range 2.3–25.6] *versus* 12.8 months [range 2.3–22.7], respectively). However, the median number of treatment cycles until the occurrence of best response was five for both groups.

Extended follow-up: time to response and duration of response

The reduction of M-protein levels over time in all responders shows that the first evidence of response was observed as early as the first cycle and that the depth of response increased over time (Figure 1). The cumulative response over time for patients who achieved a CR/VGPR is shown in Figure 2. In these patients, best responses were reported as early as cycle 3 (Figure 2), and 37% (42 of 114) of the patients achieved the response by cycle 4. Of patients who achieved a CR/VGPR as best response, 82% showed a PR at first evaluation and subsequently achieved the CR/VGPR with further treatment cycles. Of the patients who had a documented PR as their initial response, 50.5% (n=94) eventually achieved a CR/VGPR as best response with further treatment cycles. For patients who achieved an initial documented PR by cycle 4, the estimated probability of achieving a subsequent CR/VGPR was 43%, and for those achieving an initial PR by cycle 6, the probability of achieving CR/VGPR was 38%. Although the probability of a CR/VGPR decreased with delayed achievement of PR, the CR/VGPR achieved with the lenalidomide plus dexamethasone treatment regimen continued to be clinically significant. Patients who achieved a CR/VGPR as best response had a longer median duration of response compared with patients whose best response was a PR (24.0 months *versus* 8.3 months, P<0.001).

Outcomes

At a median follow-up of 48 months (data up to July 2008), 32.5% (37 of 114) of patients whose best response was a CR/VGPR and 56.0% (56 of 100) of patients who achieved PR had progressed. The median time-to-progression was significantly longer in patients whose best response was a CR/VGPR than in patients with PR as their best response (27.7 *versus* 12.0 months, P<0.001) (Table 2, Figure 3). The 1-year progression rate was 25% and 52% in patients achieving CR/VGPR and PR, respectively.

Importantly, for patients who achieved a higher quality of response, the benefit in terms of time-to-progression did not depend on when the CR/VGPR was achieved. Specifically, a comparison of time-to-progression between patients who achieved a CR/VGPR within four cycles and those who achieved the CR/VGPR after cycle 4 showed no significant difference

(hazard ratio [HR] 1.5; *P*=0.26). Likewise, time-to-progression did not differ between patients who achieved a CR/VGPR prior to cycle 6 and those who achieved the CR/VGPR after cycle 6 (HR 1.8; *P*=0.13). Of note, patients who achieved a CR/VGPR within four cycles tended to have lower β_2-microglobulin levels compared with those who achieved a CR/VGPR after cycle 4 (*P*=0.20); no other differences in baseline characteristics were noted between these two groups (*data not shown*).

At 48 months of follow-up, 59.6% (68 of 114) of patients who achieved a CR/VGPR *versus* 42% (42 of 100) of patients who had a PR remained alive. The median overall survival was significantly longer in patients whose best response was CR/VGPR than in patients whose best response was a PR (not yet reached *versus* 44.2 months, *P*=0.021) (Table 2, Figure 4).

A supportive analysis was performed using the original EBMT criteria, comparing CR/near-CR *versus* PR. Results were comparable with the analysis presented in this manuscript (*data not shown*).

Landmark analysis at 12 months

At 12 months 110 patients were included in the landmark analysis: 74 with a CR/VGPR and 36 with a PR. The median time-to-progression was significantly longer in patients who had achieved a CR/VGPR than in those who had achieved a PR (41 months *versus* 27 months; *P*=0.04). The median duration of response was also significantly longer in patients who had achieved a CR/VGPR (37 months) than in those who had achieved a PR (22 months; *P*=0.04). The 12-month landmark analysis survival rates were 70% and 56% in the CR/VGPR and PR groups, respectively. The median survival was not reached in the CR/VGPR group and was 51 months in the PR group, but this difference was not statistically significant (*P*=0.27).

Adverse events

Neutropenia and thrombocytopenia were the most common grade 3/4 adverse events among the CR/VGPR and PR groups (Table 3). Grade 3/4 deep vein thrombosis occurred in 9.6% of the CR/VGPR group and in 10% of the PR group. A total of 7.9% (n=9) of CR/VGPR group patients and 13% (n=13) of PR group patients discontinued treatment due to adverse events.

Discussion

This subanalysis of pooled data from the lenalidomide plus dexamethasone arms of two phase III multicenter, double-blind, placebo-controlled, randomized trials

Table 1. Baseline characteristics of patients who achieved a CR/VGPR or PR with lenalidomide plus dexamethasone treatment.

Characteristic	CR/VGPR (n=114)	PR (n=100)	*P* value
Median age, years (range)	64 (33–86)	62 (35–84)	0.047
Sex (M/F), %	58.8/41.2	60.0/40.0	0.890
Median time since diagnosis, years (range)	2.8 (0.5–14.6)	3.6 (0.4–14.2)	0.024
Durie-Salmon stage, n (%)			0.244
I	8 (7.0)	3 (3.0)	
II	30 (26.3)	34 (34.0)	
III	76 (66.7)	62 (62.0)	
Missing	0	1 (1.0)	
ECOG performance status score, n (%)			0.082
0	40 (35.1)	49 (49.0)	
1	54 (47.4)	43 (43.0)	
2	15 (13.2)	7 (7.0)	
Missing	5 (4.4)	1 (1.0)	
β_2-microglobulin level, n (%)			0.473
≤2.5 mg/L	37 (32.5)	38 (38.0)	
>2.5 mg/L	77 (67.5)	62 (62.0)	
N. of prior therapies, n (%)			0.038
1	29 (25.4)	13 (13.0)	
2	47 (41.2)	39 (39.0)	
3	31 (27.2)	34 (34.0)	
>3	7 (6.1)	14 (14.0)	
Type of prior therapies, n (%)			
Thalidomide	27 (23.7)	41 (41.0)	0.008
Bortezomib	10 (8.8)	7 (7.0)	0.801
Transplantation	65 (57.0)	67 (67.0)	0.008
Melphalan	53 (46.5)	42 (42.0)	0.582
Doxorubicin	54 (47.4)	58 (58.0)	0.133

CR: complete response; PR: partial response; VGPR: very good PR; ECOG: Eastern Cooperative Oncology Group.

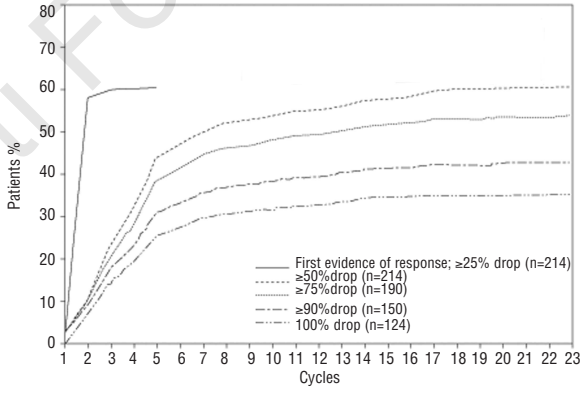

Figure 1. Accumulated maximum serum M-protein reduction after lenalidomide plus dexamethasone by treatment cycle for all patients achieving at least a partial response as best response.

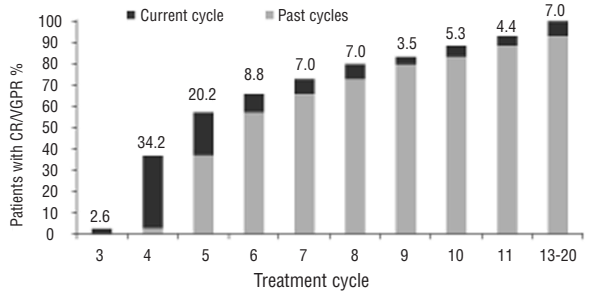

Figure 2. Cumulative response by treatment cycle for patients with complete response (CR)/very good partial response (VGPR) to lenalidomide plus dexamethasone (n=114). The numbers above the bars indicate the first occurrence of best response.

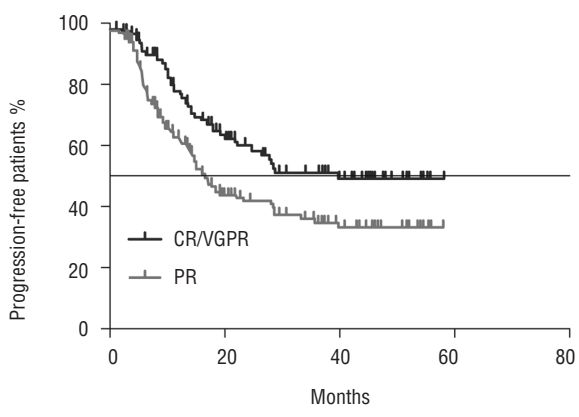

Figure 3. Kaplan-Meier estimate of time-to-progression by quality of response to lenalidomide plus dexamethasone (median follow-up of 48 months). The estimated time-to-progression for patients treated with lenalidomide plus dexamethasone in the intent-to-treat population, per quality of response group. CR: complete response; PR: partial response; VGPR: very good PR.

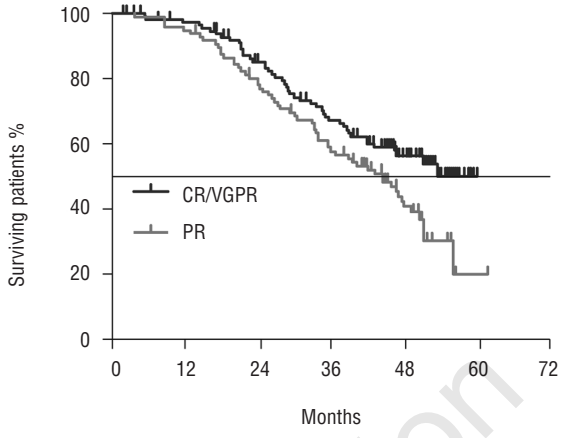

Figure 4. Kaplan-Meier estimate of overall survival by quality of response to lenalidomide plus dexamethasone (median follow-up of 48 months). The estimated overall survival for patients treated with lenalidomide plus dexamethasone in the intent-to-treat population, per quality of response group. CR: complete response; PR: partial response; VGPR: very good PR.

(MM-009 and MM-010) demonstrated that the response achieved with lenalidomide plus dexamethasone improves over time. Over 50% of patients with an initial documented PR subsequently achieved a CR/VGPR and patients who achieved a PR by cycle 6 still had a substantial probability (38%) of achieving a CR/VGPR with continued treatment. This suggests a role for improving the quality of response as a relevant treatment objective in the management of some patients with relapsed/refractory multiple myeloma.

The present analysis also demonstrated that quality of response was a prognostic factor for the most clinically relevant outcomes: time-to-progression and overall survival. At a median follow-up of 48 months, patients who achieved a CR/VGPR as best response showed significantly longer time-to-progression, duration of response, and overall survival compared to patients whose best response was a PR. The beneficial impact of CR and VGPR on patients' outcomes was first reported in the frontline setting after autologous stem cell transplantation, as reviewed recently.[16] In the relapsed setting, the correlation between quality of response and improved outcomes was previously demonstrated with bortezomib in a subanalysis of the Assessment of Proteasome Inhibition for Extending Remissions (APEX) trial.[6] Although the APEX subanalysis did not show any effect on time-to-progression, and the median overall survival was not reached, patients who achieved a CR had a significantly longer treatment-free interval and time to alternative therapy, compared with those who achieved a VGPR/PR. In the present analysis, the benefit of achieving CR/VGPR over PR on time-to-progression was maintained regardless of when the CR/VGPR was achieved.

In the last few years, CR rates have improved with the emergence of novel therapies such as bortezomib, thalidomide and lenalidomide, and can be even further improved if these drugs are used in combinations, for example bortezomib with melphalan,[17] cyclophosphamide and prednisone,[18] dexamethasone,[19] vorinostat,[20] and lenalidomide.[21] Whereas the more aggressive goal to achieve CR may be justified in high-risk patients, the impact of CR on outcomes seems to be less important in indolent disease and elderly patients, in whom the toxicity of multiple drug regimens may outweigh treatment benefits.[16]

Table 2. Time-to-progression and overall survival for patients responding to treatment with lenalidomide plus dexamethasone.

	CR/VGPR (n=114)	PR (n=100)	HR (95% CI)	Log rank *P* value
Median response duration (months)	24.0	8.3	0.449 (0.313-0.643)	<0.001
Median time-to-progression (months)	27.7	12.0	0.448 (0.313-0.641)	<0.001
Overall survival (%)	NR	44.2	0.636 (0.431-0.937)	0.021

Medians and 95% confidence intervals (CI) are based on Kaplan-Meier estimates. P values are based on two-tailed log rank tests of survival curve differences between the quality of response groups. CR: complete response; HR: hazard ratio; NR: not reached; PR: partial response; VGPR: very good PR.

A comparison between the results of landmark analysis at 12 months and the longer follow-up at 48 months showed that the benefit of achieving CR/VGPR on overall survival was observed at some point after 12 months. Taken together these results highlight the importance of continued treatment in order to achieve optimal outcomes and are in agreement with the preliminary results of a study with lenalidomide and dexamethasone which showed that continued treatment significantly predicted prolonged overall survival. Patients who had achieved a PR or better and continued treatment had an overall survival of 50.9 months compared with 35.0 months in patients who discontinued due to adverse events, withdrawal of consent, or other reasons.[22] The dose at which treatment is continued may also affect outcomes. A separate analysis showed that patients who had dose reduc-

Table 3. Grade 3 or higher adverse events occurring in at least 5% of patients responding to lenalidomide plus dexamethasone.

Adverse event	CR/VGPR, % (n=114)	PR, % (n=100)
Neutropenia	39.5	44.0
Thrombocytopenia	13.2	16.0
Anemia	11.4	8.0
Pneumonia	10.5	6.0
Deep vein thrombosis	9.6	10.0
Hyperglycemia	9.6	5.0
Hypokalemia	3.5	8.0
Asthenia	6.1	4.0
Fatigue	6.1	5.0
Muscle weakness	3.5	6.0
Lymphopenia	5.3	4.0
Leukopenia	5.3	3.0
Confusional state	5.3	2.0
Hypophosphatemia	5.3	0.0
Diarrhea	3.5	5.0
Depression	2.6	5.0
Constipation	0.9	5.0

CR: complete response; PR: partial response; VGPR: very good PR.

tions after 12 months of lenalidomide plus dexamethasone therapy experienced significantly longer progression-free survival compared to patients who required a dose reduction within the first 12 months (P=0.007).[23]

Previous reports have shown that lenalidomide plus dexamethasone is well tolerated for the treatment of patients with relapsed or refractory multiple myeloma.[9,10] In the current analysis, the longer median duration of treatment in the CR/VGPR group was not associated with more toxicity than in the PR group and the frequency of grade 3/4 adverse events was similar between these two groups.

Therefore, in the absence of disease progression and safety concerns, patients whose initial response is limited to a PR should continue lenalidomide plus dexamethasone treatment, at least as long as the best response has not yet been achieved, in order to provide the greatest opportunity to achieve the best outcomes.

Altogether, lenalidomide plus dexamethasone is a generally well-tolerated therapy, which may offer optimal benefit with continued use. To further improve the tolerability of the regimen, the dexamethasone dose can be reduced to help manage the adverse events.[24] When lenalidomide is given as continuous therapy the combination of antiproliferative and immune-stimulatory effects may allow for constant suppression of tumor regrowth. The sustained treatment effect achieved via this mechanism is demonstrated by the efficacy of single-agent lenalidomide in patients with uniformly advanced relapsed or refractory multiple myeloma (MM-014),[25] and provides an additional rationale for the study of lenalidomide in the setting of maintenance therapy. More aggressive sequential approaches using multiple drug combinations can be spared for salvage treatment. Future prospective studies are needed to understand the optimal use of multiple drug combinations and the role of maintenance therapy in the upfront and relapsed settings.

The present study is limited by the retrospective nature of the analysis. The longer overall survival and time-to-progression observed in patients who achieved a CR/VGPR compared with in those who achieved only a PR might result from a potential selection bias, since the duration of survival alone can influence the chance of a patient achieving a CR/VGPR with long-term treatment. Although the duration of treatment was slightly longer in patients who achieved a CR/VGPR than in those who had a PR, the median number of treatment cycles to best response was five cycles for both groups of patients.

Another limitation is that we did not distinguish between patients who had a near-CR and those with a VGPR (not near-CR) in our re-review of response. As discussed recently, compared with VGPR, CR is associated with a better outcome.[16] It is possible that are differences in outcomes between patients who achieve a near-CR (as utilized in the MM-009/MM-010 primary studies) and those who have a VPGR (defined simply by 90% reduction of the M-component in the serum and/or a urinary M-protein level of less than 100 mg/24 hours). However, the small numbers of patients in each of the near-CR and VGPR (not near-CR) groups precluded meaningful comparisons. Moreover, since it is difficult to separate near-CR from VGPR in cases of very small M-component spikes on electrophoresis,[16] and the level of response may not be different enough to show significantly different outcomes, we regarded near-CR and VGPR as one category as defined for the IMWG uniform response criteria.[15]

In conclusion, results from the present subanalysis indicate that the response to treatment with lenalidomide plus dexamethasone can improve over time, advocating for the continued benefit of lenalidomide beyond treating to achieve initial response. Moreover, the quality of response has a positive prognostic impact, as patients who achieved a CR/VGPR as their best response had significantly longer time-to-progression, duration of response and overall survival, compared to patients whose best response was a PR, regardless of when the CR/VGPR was achieved.

Authorship and Disclosures

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