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Multicenter, phase II study of response-adapted lenalidomide-based therapy for transplant-ineligible patients with newly diagnosed multiple myeloma without high-risk features

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ABSTRACT

Lenalidomide and low-dose dexamethasone (Rd) are a standard treatment for older adults with multiple myeloma (MM). Lenalidomide monotherapy has rarely been evaluated for newly diagnosed transplant-ineligible MM patients. This multicenter phase II trial evaluated a response-adapted strategy for elderly

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patients with newly diagnosed MM without high-risk features. Patients were administered single-agent lenalidomide for the first 21 days of two 28-day cycles. Patients with progressive disease received Rd. The primary endpoint was progression-free survival using the uniform response assessment from the International Myeloma Working Group . Of the 34 enrolled patients, 28 were included in the efficacy analysis. The overall response rate (ORR, ≥ partial response [PR]) to single-agent lenalidomide or lenalidomide plus prednisone was 64.3%. Ten patients received Rd after disease progression, with an Rd ORR of 70%. The ORR of response-adapted lenalidomide-based therapy was 75%. After the median follow-up of 35.6 months, the median progression-free survival was 33.5 months (95% confidence interval [CI], 16.9-50.2), and the median overall survival was 51.8 months (95% CI, 22.0-81.6). The most common adverse event was neutropenia (46.7%), and 17 patients (56.7%) experienced infection including pneumonia. Response-adapted lenalidomide-based therapy was feasible in newly diagnosed, transplant-ineligible MM patients without high-risk features.

ARTICLE INFO

Keywords: Myeloma; Older adults; Lenalidomide; Corticosteroids; Response-adapted therapy

Introduction

Multiple myeloma (MM) is a malignant neoplasm of proliferative monoclonal plasma cells producing a monoclonal protein. The disease can manifest in individuals of all ages but primarily affects elderly patients.[1,2] The initial treatment of MM in the elderly is often challenging due to their frailty, comorbidities, impaired organ function, and altered pharmacodynamics that increase the risk of infection and other complications during chemotherapy.[3]

Historically, combination chemotherapy based on a backbone of melphalan plus prednisone (MP) has been the standard treatment for elderly patients with newly diagnosed MM ineligible for high-dose chemotherapy and autologous stem cell transplantation.[4] In the era of novel agents, proteasome inhibitor bortezomib plus MP (VMP) demonstrated superior response rates and longer survival than those for MP alone in patients with transplant-ineligible untreated MM, although with increased rates of grade 3 or 4 peripheral neuropathy and gastrointestinal adverse events (AEs).[5,6]

Lenalidomide, an immunomodulatory drug, showed efficacy in combination with dexamethasone for relapsed or refractory MM and was approved by the Food and Drug Administration and the European Medicines Agency.[7,8] In the randomized phase 3 FIRST trial, continuous lenalidomide and low-dose dexamethasone (Rd) demonstrated superior outcomes to that for MP plus thalidomide (MPT) among patients with newly diagnosed MM who were ineligible for stem cell transplantation.[9] Based on these results, low-dose dexamethasone (40 mg a week) in combination with lenalidomide has become a standard-of-care for older patients with newly diagnosed MM.[10] However, the addition of dexamethasone to lenalidomide, especially in early trials with high-dose dexamethasone, was associated with significant AEs, including infections, hyperglycemia, and deep vein thrombosis.[7,8] In a phase 3 trial (ECOG E4A03) comparing lenalidomide plus high-dose dexamethasone (40 mg on days 1-4, 9-12, and 17-20 of each cycle) to lenalidomide plus low-dose dexamethasone (40 mg on days 1, 8, 15, and 22 of each cycle), lenalidomide plus low-dose dexamethasone was associated with better short-term overall survival (OS) and had lower toxicity in patients with newly diagnosed MM.[11]

In contrast to the efforts to maximize therapeutic capacity and increase effectiveness, a small number of trials have assessed methods to reduce AEs caused by high-dose corticosteroids. A multicenter, single-arm study of lenalidomide monotherapy in 222 patients with relapsed or re-

fractory MM reported an overall response rate (ORR) of 26% and progression-free survival (PFS) of 4.9 months[12]. Baz et al. retrospectively analyzed the activity of single-agent lenalidomide in newly diagnosed symptomatic MM patient[13], reporting that lenalidomide was generally well tolerated and no grade 4 hematologic toxicities. The ORR to single-agent lenalidomide was 47% and a minor response was observed in 76% of cases. Except for these studies, however, intermediate doses and schedules of corticosteroids combined with lenalidomide have not been evaluated. Thus, the optimal dose and schedule of lenalidomide plus dexamethasone were unclear.

This multicenter, phase II trial evaluated a response-adapted strategy using single-agent lenalidomide for elderly patients with newly diagnosed MM without high-risk features and optimized the dose and schedule for corticosteroids in the frontline therapy.

Patients and methods

Patients and treatment

Eligible patients included those who were older, with newly diagnosed MM not able to receive high-dose chemotherapy and autologous stem cell transplantation. The patient inclusion criteria were as follows: (a) symptomatic MM; (b) age 65 years or above (c) Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1; (d) measurable disease, defined as serum M protein level $\geq$5.0 g/L, urine M spike $\geq$200 mg/24 h, or involved free light chain (FLC) $\geq$100 mg/L with abnormal FLC ratio; (e) adequate hematologic and organ function (hemoglobin concentration >8.0 g/dL, absolute lymphocyte count $\geq$1.0 $\times$ 9 10^9 cells/L, platelet count $\geq$100 $\times$ 10^9/L, and calculated creatinine clearance $\geq$30 m:/min).

Patients were ineligible if they had deletion 17p, t(4;14), t(14;16), t(14;20); deletion 13 by metaphase cytogenetics (deletion 13 by fluorescence in situ hybridization [FISH] was allowed); aneuploidy by metaphase cytogenetics; or International Staging System (ISS) stage III disease. However, patients with other high-risk features, such as trisomy or tetrasomy 1q, elevated lactate dehydrogenase (LDH) or extramedullary disease, were not excluded. Patients were required to be able to understand and sign an informed consent document. The study was approved by the Institutional Review Board of each institution.

Fig. 1 shows a schematic of the study protocol. Patients were treated with lenalidomide monotherapy (25 mg daily for the first 21 days of each 28-day cycle) without administration of corticosteroids. Patients with a creatinine clearance of 30-60 mL/min could be started on lenalidomide at 10 mg, with a possible dose increase to 15 mg at cycle 3 if significant toxicities did not occur. If patients had a minimal response (MR) or better after 2 cycles of single-agent lenalidomide, they continued lenalidomide monotherapy until progression. If patients had stable disease (SD) after 2 cycles, 100 mg prednisone was added on days 1-5 of each cycle. In the event of progressive disease (PD) on lenalidomide monotherapy or lenalidomide plus prednisone, patients received 40 mg of dexamethasone every week, simultaneously with lenalidomide. Patients treated with combined lenalidomide and dexamethasone who developed PD at any time were removed from the study. Patients received appropriate thromboprophylaxis (aspirin or anticoagulants) at the discretion of the treating physicians. Other supportive care measures, including bisphosphonates, antibiotics, and erythropoietin-stimulating agents, were allowed, per standard of care.

This study was designed as a pair of trials. Ours was a multicenter phase II trial in Korea; a paired study was simultaneously conducted under the same protocol as a single-center phase II trial at the H. Lee Moffit Cancer Center and Research Institute, Tampa, FL, USA.

Assessment

Disease assessments were initially performed monthly; however, patients who completed the first 6 cycles of therapy could undergo disease assessments every 3 months as long as they were on a stable dose of lenalidomide for more than 2 cycles and were responding to therapy.

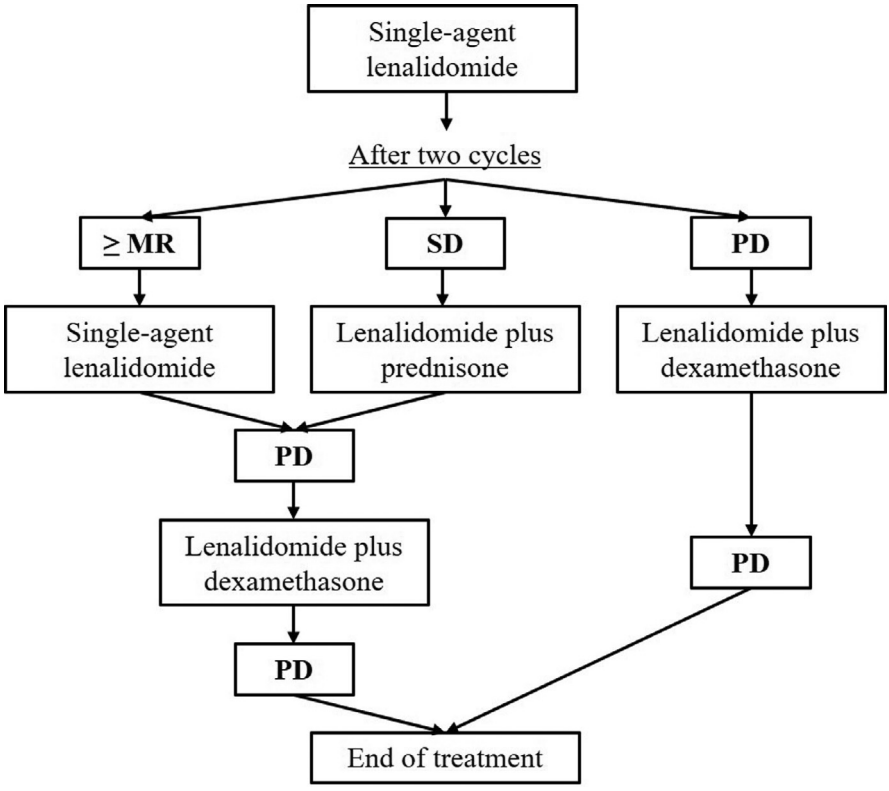

Fig. 1. Study design of the response-adapted strategy.
MR, Minimal response; SD, Stable disease; PD, Progressive disease.

The study used the uniform response assessment of the International Myeloma Working Group (IMWG) with the addition of MR[14]. MR was defined as a 25%-49% decrease in serum M spike and a 50%-89% improvement in urine M spike. For patients without measurable serum or urine M spikes, a 25%-49% decrease in the difference between involved and uninvolved free light chains was required. We collected data on AEs every cycle while on treatment and again at the end of treatment. All AEs were initially graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.

Statistical analysis

The primary endpoint of this study was PFS of response-adapted therapy, defined as the time from single-agent lenalidomide start to the failure of combined Rd or death. The secondary endpoints were the response rates of single-agent lenalidomide and response-adapted therapy, the PFS of single-agent lenalidomide, OS of response-adapted therapy, and safety profile.

The differences between groups were assessed using Student's t-tests for continuous variables. Comparisons of dichotomous or categorical variables were based on Pearson's chi-squared or Fisher's exact tests. The Kaplan–Meier method was used to evaluate PFS and OS. PFS and OS were compared using log-rank tests. The Cox proportional hazards model was used for multivariate analysis. All *P*-values were 2-tailed. *P*-values less than 0.05 were considered significant. All data were analyzed using IBM SPSS Statistics for Windows, version 23.0 (IBM Corp.).

Table 1
Patient characteristics ($N = 28$).

	L or LP ($N = 18$)	LD ($N = 10$)	Entire ($N = 28$)	*P*-value
Age, years				0.174
Mean (SD)	71.6 (6.3)	67.8 (7.6)	70.2 (6.9)	
Median (range)	70.5 (55–81)	69 (48–76)	70 (48–81)	
Sex				1.000
Male	8 (44.4%)	5 (50%)	13 (46.4%)	
Female	10 (55.6%)	5 (50%)	15 (53.6%)	
ISS				1.000
Stage I	6 (33.3%)	4 (40%)	10 (35.7%)	
Stage II	12 (66.7%)	6 (60%)	18 (64.3%)	
R-ISS				0.674
Stage I	4 (22.2%)	3 (30%)	7 (25%)	
Stage II	14 (77.8%)	7 (70%)	21 (75%)	
ECOG performance status				1.000
0	4 (22.2%)	2 (20%)	6 (21.4%)	
1	14 (77.8%)	8 (80%)	22 (78.6%)	
β2-microglobulin, μg/L				0.178
Mean (SD)	3.4 (1.0)	2.8 (1.1)	3.2 (1.1)	
Median (range)	3.6 (1.8–5.1)	2.7 (1.4–4.8)	3.4 (1.4–5.1)	
Albumin, g/dL				0.905
Mean (SD)	3.4 (0.88)	3.4 (0.82)	3.4 (0.85)	
Median (range)	3.4 (2.0–4.8)	3.5 (1.9–4.7)	3.4 (1.9–4.8)	
Creatinine, g/dL				0.888
Mean (SD)	0.93 (0.32)	0.91 (0.43)	0.92 (0.36)	
Median (range)	0.8 (0.56–1.6)	0.8 (0.44–1.9)	0.8 (0.44–1.9)	
Cytogenetics				
Complex karyotypes	2 (11.1%)	2 (20%)	4 (14.3%)	
Trisomy 18	1 (5.6%)	-	1 (3.6%)	
Trisomy 1q	-	1 (10%)	1 (3.6%)	

ECOG, Eastern Cooperative Oncology Group; ISS, International Staging System; L, Single-agent lenalidomide; LD, Lenalidomide plus dexamethasone; LP, Lenalidomide plus prednisone; SD, Standard deviation; R-ISS, Revised International Staging System.

Results

Patients and treatment

From July 2010 to August 2012, 34 eligible patients were enrolled at 13 centers in Korea. Of them, 28 patients were included in the efficacy analysis after excluding 6 patients. Five patients who did not complete 2 cycles of therapy and repeat paraprotein assessments were excluded from the efficacy analysis as the response could not be determined. One patient withdrew informed consent during the first cycle of treatment. The patient characteristics are shown in Table 1. The median age was 70 years (range, 48-81 years) and 13 patients (46.4%) were male. Eighteen patients (64.3%) were ISS stage II and 21 (75%) were revised ISS stage II. Twenty-two patients (78.6%) had an ECOG performance status of 1. Concerning cytogenetics by chromosome and FISH, 4 patients (14.3%) had complex karyotypes, one patient had trisomy 18, and one patient had trisomy 1q.

Efficacy

Twenty-eight patients who were treated with single-agent lenalidomide for more than 2 cycles were enrolled in the efficacy analysis. Of them, 10 patients received additional dexamethasone with lenalidomide after developing PD during single-agent lenalidomide or lenalidomide plus prednisone, per the study protocol. The best responses to single-agent lenalidomide or response-adapted therapy according to the uniform response assessment from the IMWG are

Table 2
Best response to single-agent lenalidomide or response-adapted strategy according to the uniform response assessment from the International Myeloma Working Group (IMWG).

	L or LP (N = 28)	LD (N = 10)	Best response to response-adapted therapy (N = 28)
PD, N (%)	1 (3.6%)	-	-
SD, N (%)	4 (14.3%)	-	2 (7.1%)
MR, N (%)	5 (17.9%)	3 (30%)	5 (17.9%)
PR, N (%)	13 (46.4%)	4 (40%)	14 (50%)
VGPR, N (%)	-	-	-
CR, N (%)	5 (17.9%)	3 (30%)	7 (25%)
ORR, N (%)	18 (64.3%)	7 (70%)	21 (75%)

CR, Complete response; MR, Minimal response; L, Single-agent lenalidomide; LD, Lenalidomide plus dexamethasone; LP, Lenalidomide plus prednisone; ORR, Overall response rate; PD, Progressive disease; PR, Partial response; SD, Stable disease; VGPR, Very good partial response.

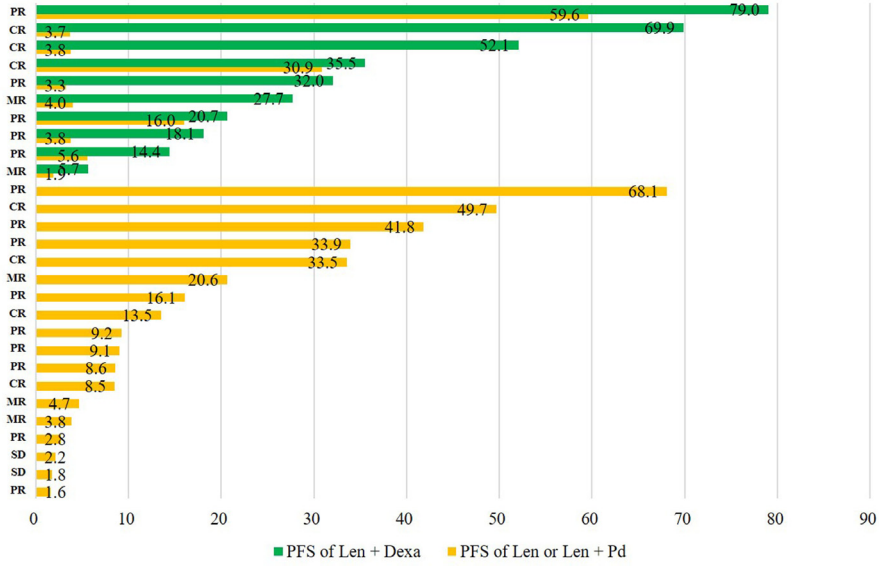

Fig. 2. Best response and duration of progression-free survival (PFS) of each patient.

summarized in Table 2. The best responses to single-agent lenalidomide or lenalidomide plus prednisone were MR (5 patients, 17.9%), partial response (PR) (13 patients, 46.4%), and complete response (CR) (5 patients, 17.9%). No very good partial response (VGPR) was reported. The ORR to single-agent lenalidomide or lenalidomide plus prednisone was 64.3%. Of the 10 patients who received lenalidomide plus dexamethasone per protocol, 3 (30%) showed MR, 4 (40%) had PR, and 3 (30%) achieved CR after the addition of dexamethasone to lenalidomide. Combining those therapeutic approaches, the overall best response was SD in 2 patients (7.1%), MR in 5 patients (17.9%), PR in 14 patients (50%), and CR in 7 patients (25%). No VGPR was observed among any patients per protocol. The ORR of response-adapted lenalidomide-based therapy was 75%.

With a median follow-up of 35.6 months, 14 patients (50%) showed PD during single-agent lenalidomide or lenalidomide plus prednisone treatment; of these, dexamethasone was added to lenalidomide in 10 patients. The best response and PFS for each patient are shown in Fig. 2. The median PFS of patients administered single-agent lenalidomide or lenalidomide plus prednisone (N = 18) and lenalidomide plus dexamethasone (N = 10) were 33.9 months (yellow line, 95% confidence interval [CI] 11.1-56.8) and 32.0 months (green line, 95% CI 12.1-51.9; P = 0.606),

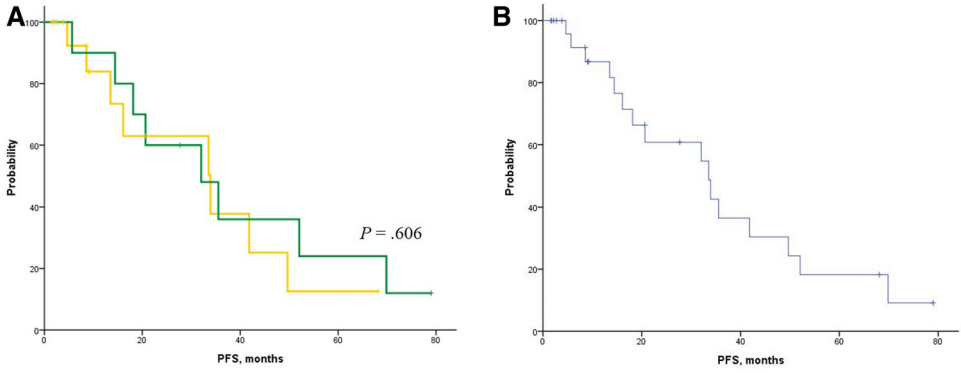

Fig. 3. Progression-free survival (PFS) of single-agent lenalidomide or lenalidomide plus prednisone ($N = 18$, yellow line, median 33.9 months, 95% confidence interval [CI] 11.1-56.8) and lenalidomide plus dexamethasone ($N = 10$, green line, median 32.0 months, 95% CI 12.1-51.9; $P = 0.606$) (A), as well as PFS for all patients ($N = 28$, median 33.5 months, 95% CI 16.9-50.2) (B). (Color version of figure is available online.)

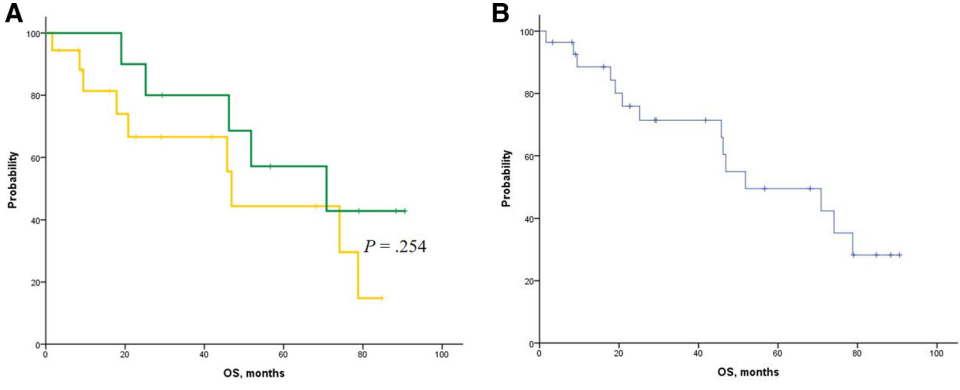

Fig. 4. Overall survival (OS) of single-agent lenalidomide or lenalidomide plus prednisone ($N = 18$, yellow line, median 46.9 months, 95% confidence interval [CI] 43.8-19.9) and lenalidomide plus dexamethasone ($N = 10$, green line, median 70.8 months, 95% CI 25.3-116.4; $P = 0.254$) (A), and OS of all patients ($N = 28$, median 51.8 months, 95% CI 22.0-81.6) (B). (Color version of figure is available online.)

respectively (Fig 3A). The median PFS for all patients ($N = 28$) was 33.5 months (95% CI 16.9-50.2; Fig 3B).

As of the cut-off date for survival follow-up (January 2018), 14 patients had died, 5 patients were alive, and nine patients were lost to follow-up. Three of the deaths occurred before confirmation of PD. Two patients in PR died due to acute myocardial infarction and pneumonia, respectively. Another patient with CR died from unknown causes. The median OS of patients administered single-agent lenalidomide or lenalidomide plus prednisone ($N = 18$) and lenalidomide plus dexamethasone ($N = 10$) were 46.9 months (yellow line, 95% CI 43.8-49.9) and 70.8 months (green line, 95% CI 25.3-116.4; $P = 0.254$), respectively (Fig 4A). The median OS of all patients ($N = 28$) was 51.8 months (95% CI 22.0-81.6; Fig 4B).

Safety

Safety analysis was performed in 30 patients. The hematologic and non-hematologic AEs are shown in Table 3. The most common hematologic AE was neutropenia ($N = 14$, 46.7%). Eleven events (36.7%) were ≥grade 3 and 2 patients (6.7%) experienced neutropenic fever. Three events (10%) of anemia ≥grade 3 and 3 events (10%) of thrombopenia ≥grade 3 were observed. The

Table 3
Hematologic and nonhematologic adverse events, regardless of attribution ($N = 30$).

Adverse events (AEs)	Grade 1–2	≥Grade 3	All grades
Hematologic AEs			
Neutropenia	3 (10%)	11 (36.7%)	14 (46.7%)
Anemia	2 (6.7%)	3 (10%)	5 (16.7%)
Thrombocytopenia	2 (6.7%)	3 (10%)	5 (16.7%)
Neutropenic fever		2 (6.7%)	2 (6.7%)
Nonhematologic AEs			
Abdominal pain	2 (6.7%)	0	2 (6.7%)
Adrenal insufficiency	0	1 (3.3%)	1 (3.3%)
Anorexia	9 (30%)	1 (3.3%)	10 (33.3%)
Constipation	6 (20%)	0	6 (20%)
Cough	3 (10%)	0	3 (10%)
Diarrhea	2 (6.7%)	3 (10%)	5 (16.7%)
Dizziness	5 (16.7%)	2 (6.7%)	7 (23.3%)
Dyspnea	4 (13.3%)	0	4 (13.3%)
Edema	4 (13.3%)	0	4 (13.3%)
Elevated liver enzyme	0	2 (6.7%)	2 (6.7%)
Fatigue	2 (6.7%)	2 (6.7%)	4 (13.3%)
Fever	3 (10%)	0	3 (10%)
Hyperglycemia	1 (3.3%)	0	1 (3.3%)
Ileus	0	1 (3.3%)	1 (3.3%)
Infection	9 (30%)	8 (26.7%)	17 (56.7%)
Insomnia	2 (6.7%)	0	2 (6.7%)
Itching	3 (10%)	0	3 (10%)
Mucositis	2 (6.7%)	0	2 (6.7%)
Myocardial ischemia	1 (3.3%)	1 (3.3%)	2 (6.7%)
Myalgia	2 (6.7%)	0	2 (6.7%)
Nausea	3 (10%)	0	3 (10%)
Neurologic deficit	2 (6.7%)	0	2 (6.7%)
Neuropathy	0	1 (3.3%)	1 (3.3%)
Pain	9 (30%)	0	9 (30%)
Pneumonitis	0	2 (6.7%)	2 (6.7%)
Pulmonary edema	2 (6.7%)	0	2 (6.7%)
Rash	7 (23.3%)	0	7 (23.3%)
Venous thrombosis	0	2 (6.7%)	2 (6.7%)
Vomiting	5 (16.7%)	1 (3.3%)	6 (20%)
Serious AEs			4 (13.3%)

most common nonhematologic AE, regardless of grade or attribution, was infection ($N = 17$, 56.7%), followed by anorexia ($N = 10$, 33.3%) and pain ($N = 9$, 30%). Eight infection events (26.7%) were ≥grade 3. Two cases of myocardial ischemia (6.7%) were noted and one patient died from acute myocardial infarction. Two patients (6.7%) experienced venous thrombosis ≥grade 3 and no hyperglycemia ≥grade 3 was observed. Among hematologic and non-hematologic AEs, 4 serious AEs (13.3%) were noted. Dose reduction and delay of lenalidomide was observed in 14 and 8 patients, respectively. The dose reduction of lenalidomide was mainly due to cytopenia, 5 patients with ≥grade 3 neutropenia and 2 patients with grade 4 thrombocytopenia.

Discussion

The median PFS of response-adapted lenalidomide-based therapy, a primary endpoint of our study, was 33.5 months, with a corresponding ORR of 75%. The ORR for single-agent lenalidomide or lenalidomide plus prednisone was 64.3%, and only 10 patients (35.7%) treated with lenalidomide received additional low-dose dexamethasone per protocol by PD.

The efficacy of single-agent lenalidomide and response-adapted approach is impressive compared to the results of the FIRST trial[9], even considering our exclusion of patients with high-risk cytogenetics and ISS stage III. The median PFS of the continuous lenalidomide-dexamethasone

group in the FIRST trial was 25.5 months, compared to 33.5 months in our study. Most recently, efficacy of Rd in front-line from a pooled meta-analysis of 3 phase III trials (FIRST, MAIA, and SWOG S0777) was reported[15]. The median PFS and OS with Rd were estimated to be 28.9 months (95% CI 26.8-31.3) and 67.2 months (95% CI 61.3-74.2), respectively. In particular, the MAIA study had the longest median PFS of Rd (31.9 months)[16], and the authors of this study suggested that the longer PFS in recent studies may reflect the increased clinical experience with Rd. The incidence of ≥grade 3 infection in our study was similar to that in the continuous lenalidomide-dexamethasone group in the FIRST trial (26.7% vs 29%); however, we observed no ≥grade 3 hyperglycemia (vs 5% in the continuous lenalidomide-dexamethasone group in the FIRST trial). The results of the VISTA study indicated a median time to progression of 27.2 months for the VMP regimen and an ORR of 71% (PR or better).[5,17] The on-study death and treatment discontinuation rates of VMP were 6% and 15%, respectively, in that trial, with high rates of grade 3 or 4 thrombocytopenia, neutropenia, and peripheral sensory neuropathy.[18] Concerning AEs, a response-adapted therapy starting from single-agent lenalidomide is an option for frail patients with MM without high-risk features.

According to 2012 Korean national cancer statistics, the incidence of MM had increased 2-fold over the last 10 years. The proportion of the population aged ≥65 years has increased gradually and the median age of MM patients in Korea was 68 years[19]. This study was conducted as a pair of trials; a multicenter study in Korea and a single-center study at the H. Lee Moffit Cancer Center and Research Institute in Tampa, FL, USA.[20] The US single-center study enrolled 27 patients with newly diagnosed MM without high-risk cytogenetics, with a median age of 75 years. Nine patients received additional dexamethasone per protocol. The ORR of response-adapted therapy was 74% and the median PFS and OS were 36 and 65 months, respectively. In comparison to this single-center study, the 13 participating centers in Korea each enrolled 1–5 patients. This was meaningful because not only were the findings more generalizable due to the multicenter nature of the trial, but also the efficacy and tolerability of a response-adapted lenalidomide-based strategy were evaluated in older Asian patients, who are particularly susceptible to chemotherapy.[21] The most common AE in both studies was neutropenia, with a higher incidence in the US single-center study (81% of all grades and 67% of grade 3 or 4). Of 34 patients who started single-agent lenalidomide in our study, 6 were excluded from the efficacy analysis; 5 dropped out before 2 cycles of treatment due to AEs and one patient withdrew informed consent. The ORR and PFS were similar between studies; however, the OS of our patients was shorter than that in patients at the H. Lee Moffit Cancer Center (52 vs 65 months). The shorter OS in our study was due to the loss of follow-up for some patients after completing treatment and reduced availability of novel drugs and effective clinical trials of second or higher lines of therapy due to regional situations in Korea.

Various triplet regimens are preferred for front-line treatment of transplant-ineligible MM patients. [10] Proteasome inhibitors, bortezomib, carfilzomib, and ixazomib have been tried in combination with a backbone of lenalidomide plus dexamethasone in less frail patients,[22-24] while 2-drug regimens are reserved for older and frailer patients. Daratumumab, a human IgGκ monoclonal antibody that targets CD38, is another component of induction and maintenance therapy for patients with MM who are not eligible for high-dose chemotherapy and stem cell transplantation.[25] As daratumumab has direct antitumor activity and an immunomodulatory component that results in depletion of immunosuppressive CD38-expressing regulatory T cells,[26] it has been investigated as both a monotherapy and in combination with standard-of-care. Most recently, a randomized phase III trial with daratumumab plus lenalidomide and dexamethasone (DRd) demonstrated a significantly lower risk of disease progression and higher CR rate compared to that for the doublet of lenalidomide and dexamethasone for newly diagnosed MM patients ineligible for stem cell transplantation.[16] However, patients in this trial administered DRd had a higher incidence of neutropenia (50% with grade 3 or 4) and infection including pneumonia (13.7% with grade 3 or 4). The alternative daratumumab-containing regimen for transplant-ineligible older patients was daratumumab plus VMP (D-VMP). A randomized, phase 3 trial (ALCYONE) reported 90.9% ORR and a median PFS of 36.4 months (95% CI 32.1-45.9) in patients treated with D-VMP.[27,28] Despite the remarkable efficacy of D-VMP, the infection rate was higher

(23.1% grade 3 or 4 in the D-VMP group vs. 14.7% grade 3 or 4 in the VMP group). To reduce the risk of infection and other complications of corticosteroids while maximizing treatment efficacy, steroid-sparing regimens containing novel immunotherapeutic drugs could be promising strategies for more vulnerable patients.

In conclusion, single-agent lenalidomide and subsequent addition of dexamethasone according to the response showed acceptable efficacy and toxicity in front-line treatment for elderly patients with MM without high-risk features. This response-adapted lenalidomide-based therapy is an option for older and frail patients who are not eligible for high-dose chemotherapy and autologous stem cell transplantation. Since the small sample size was the main limitation of this study, prospective studies involving larger patient numbers are warranted to provide additional evidence.

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Ethical approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.

Conflict of interest

RB received research funding from Celgene, Karyopharm, Abbvie, Merck, and Sanofi; is on the advisory boards of Celgene, Karyopharm, and Sanofi; and has received honoraria from GSK. The other authors declare that they have no conflict of interest.

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