Received: 6 November 2019 | Revised: 21 December 2019 | Accepted: 3 January 2020

DOI: 10.1002/ajh.25726

RESEARCH ARTICLE

Pomalidomide, cyclophosphamide, and dexamethasone for elderly patients with relapsed and refractory multiple myeloma: A study of the Korean Multiple Myeloma Working Party (KMMWP-164 study)

Ho Sup Lee[1] | Kihyun Kim[2] | Seok Jin Kim[2] | Je-Jung Lee[3] | Inho Kim[4] | Jin Seok Kim[5] | Hyeon-Seok Eom[6] | Dok Hyun Yoon[7] | Cheolwon Suh[7] | Ho-Jin Shin[8] | Yeung-Chul Mun[9] | Min Kyoung Kim[10] | Sung-Nam Lim[11] | Chul Won Choi[12] | Hye Jin Kang[13] | Sung-Soo Yoon[4] | Chang-Ki Min[14] the Korean Multiple Myeloma Working Party (KMMWP)

[1]Department of Internal Medicine, Kosin University College of Medicine, Busan, South Korea

[2]Department of Medicine, Samsung Medical Center, Sunkyunkwan University School of Medicine, Seoul, South Korea

[3]Department of Hematology-Oncology, Chonnam National University Hwasun Hospital, Hwasun, Jeollanam-do, South Korea

[4]Department of Internal Medicine, Seoul National University Hospital, Seoul, South Korea

[5]Division of Hematology, Department of Internal Medicine, Severance Hospital, Yonsei University College of Medicine, Seoul, South Korea

[6]Department of Internal Medicine, National Cancer Center of Korea, Goyang, South Korea

[7]Department of Oncology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

[8]Department of Internal Medicine, Pusan National University Hospital, Busan, South Korea

[9]Department of Internal Medicine, Ewha Womans University School of Medicine, Seoul, South Korea

[10]Department of Medicine, Yeungnam University College of Medicine, Daegu, South Korea

[11]Department of Internal Medicine, Haeundae Baek Hospital, Busan, South Korea

[12]Division of Hematology-oncology, Department of Internal Medicine, Korea University Guro Hospital, Seoul, South Korea

[13]Department of Hemato-Oncology, Korea Institute of Radiological and Medical Sciences, Seoul, South Korea

[14]Department of Internal Medicine, Seoul St. Mary's Hospital, Catholic University of Korea, Seoul, South Korea

Correspondence
Chang-Ki Min, Hematology, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea, 505, 222 Banpo-daero, Seocho-gu, Seoul 06591, South Korea.
Email: ckmin@catholic.ac.kr

Sung-Soo Yoon, Department of Internal Medicine, Seoul National University Hospital, Seoul, Republic of Korea, 101, Daehak-ro, Jongno-gu, Seoul 03080, South Korea.
Email: ssysmc@snu.ac.kr

Abstract

Patients with transplant-ineligible relapsed and refractory multiple myeloma (RRMM) have a short life expectancy, especially when they have failed both the proteasome inhibitor and immunomodulator therapies. This study aimed to assess the efficacy and safety of pomalidomide, cyclophosphamide, and dexamethasone (PCd) in elderly patients with RRMM. This phase 2 clinical trial recruited 55 elderly patients with RRMM. The patients underwent a 28-day treatment cycle: pomalidomide (4 mg/day on days 1-21, administered orally) and cyclophosphamide (400 mg/day on days 1, 8, and 15; administered orally) plus dexamethasone. The median (range) age of the patients was 73.3 (64-86) years, and 8 (14.5%) patients who were ≥ 80 years old. Eight (14.5%) and 31 (56.4%) patients exhibited stage III (revised international staging system) and frail status (simplified frailty scale), respectively. The overall response rate (ORR) and clinical benefit rate (CBR) of PCd therapy were 58.2% and 72.7%,

respectively. The median PFS and median overall survival (OS) were 6.90 months (95% CI, 4.7-9.0) and 18.48 months (95% CI, 9.4-27.6), respectively. The incidence rate of grade ≥ 3 non-hematological toxicities was 70.8%. In particular, the incidence rate of primary infection was 45.4%, including 21.8% for pneumonia, 9.0% for sepsis, and 14.6% for febrile neutropenia. In conclusion, PCd is an effective regimen for elderly patients with RRMM who had failed both bortezomib and lenalidomide treatments, but in whom the treatment-associated infection is the main cause of morbidity and mortality.

1 | INTRODUCTION

Over the last few years, there has been a marked improvement in the survival outcomes of patients with multiple myeloma (MM). This is mainly due to the development of novel therapeutic agents, such as first-in-class proteasome inhibitor (bortezomib) and immunomodulatory drugs (IMiDs) for relapse and refractory MM (RRMM).[1,2] However, patients with RRMM who have undergone multiple lines of therapy exhibit a poor prognosis.[3] There was a rapid increase in the number of patients with RRMM who were refractory to bortezomib and lenalidomide. Thus, second generation IMiDs were developed and approved for treating RRMM. Previously, the combination of pomalidomide, cyclophosphamide, and dexamethasone (PCd) was used to treat patients with RRMM who were not responsive to at least two prior treatments with bortezomib and lenalidomide.[4,5] However, there was a need for improving the treatment efficacy for RRMM. Hence, pomalidomide in combination with other drugs, such as bortezomib, carfilzomib, or daratumumab was evaluated for treating RRMM.[6-10] These drug combinations exhibited good treatment response rates and improved the survival outcomes of patients. These regimens have been fully approved and are considered a new standard of care for patients with RRMM. Recently, the combinations of elotuzumab (ELOQUENT-3) or isatuximab (ICARIA) plus pomalidomide and dexamethasone (PomDex) have resulted in good treatment outcomes in patients with MM, in whom the treatment with lenalidomide and proteasome inhibitor had failed.[9,11] Now, novel agents in combination with PomDex may be beneficial but are too costly. These combination therapies can increase the cost of the drugs as compared to that of the PomDex or PCd regimen. However, there are no data comparing the cost-effectiveness of PCd with that of other combination treatments with pomalidomide or other novel therapeutic agents. Pelligra et al reported that PomDex may be a cost-effective treatment option relative to daratumumab or carfilzomib monotherapy in patients that were heavily pretreated with RRMM.[12] On the contrary, Gong et al have presented different results, showing that daratumumab is costeffective for RRMM as compared to pomalidomide.[13]

Globally, the median age at which MM is diagnosed is around 70 years. Most patients with RRMM are diagnosed at the age of 75 to 80 years when they are frail. The multidrug combination therapy paradigm increases drug toxicity, which can be a limiting factor for treating elderly patients with RRMM. Additionally, the effectiveness of combination therapy has not been demonstrated in elderly patients with RRMM. The efficacy of PCd therapy may not be markedly different from that of other reported therapies based on triplet PomDex combination with novel therapeutic agents. However, the safety profile of the triplet combination remains unclear, particularly in elderly patients with RRMM. The efficacy of PCd therapy among elderly patients with RRMM who are not responsive to bortezomib and lenalidomide treatments has not also been evaluated. Hence, this study aimed to evaluate the efficacy and safety of PCd therapy in elderly patients with RRMM who had failed to prior bortezomib and lenalidomide treatments.

2 | METHODS

2.1 | Patients

This open-label, multicenter, non-randomized phase 2 trial was undertaken in 14 centers in South Korea between May 2015 and November 2017. The eligible patients had undergone two or more prior lines of therapy, including both bortezomib and lenalidomide in combination with bortezomib, melphalan, and prednisone (VMP) as the front-line therapy. This was followed by lenalidomide and dexamethasone (Rd) or thalidomide-containing treatment as the second line or more, in accordance with Health Care Insurance System of South Korea. The relapsed and refractory (Rel/Ref) disease was defined following the International Myeloma Working Group (IMWG) guidelines.[3,14] The primary end-point of the study was median progression-free survival (PFS). The secondary response and survival rates were assessed according to the IMWG criteria.[3,14] Additionally, measurable disease was defined by the presence of one of the following parameters: serum monoclonal protein ≥0.5 g/dL; urine monoclonal protein >200 mg/24 h; or serum free light chain ≥10 mg/dL and abnormal serum free light chain ratio. The patients exhibited an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2 and serum creatinine levels of <3 mg/dL. Cytogenetic risk was determined by the conventional cytogenetics or fluorescence in situ hybridization (FISH). The high risk factors included t(4;14), 17p deletion, t(14;16), t(14;20), gain(1q), del (13), and nonhyperdiploidy, whereas standard risk factors included t(11;14), t(6;14) and all the others.[15]

TABLE 1 The clinical characteristics of patients enrolled in this study

Variables		All patients (*N* = 55)
Age (years)	median [range]	73.3 [64.4-85.6]
	≥80	8 (14.5)
	<80	47 (85.5)
Sex (%)	Male	33 (60.0)
	Female	22 (40.0)
ECOG (%)	0	13 (23.6)
	1	34 (61.8)
	2	8 (14.5)
Comorbidity (%)	<2	37 (67.3)
	≥2	18 (43.6)
Frailty	Nonfrail	24 (32.7)
	Frail	31 (56.4)
Subtype (%)	IgG, κ or λ	22 (40.0)
	IgA, κ or λ	10 (18.2)
	Light chain disease	7 (12.7)
	Others	3 (5.5)
	NA	13 (23.6)
β_2MG (mg/L)	median [range]	3.6 [1.7-17.6]
CrCl (mL/min)	median [range]	54.1 [15.6-102.6]
LDH (%)	Normal	29 (55.8)
	Abnormal	19 (36.5)
	NA	4 (7.7)
Cytogenetic risk (%)	Standard	33 (60.0)
	High	11 (20.0)
	NA	11 (20.0)
ISS (%)	Stage I	20 (36.4)
	Stage II	17 (30.9)
	Stage III	14 (25.5)
	NA	4 (7.3)
R-ISS (%)	Stage I	13 (23.6)
	Stage II	30 (54.5)
	Stage III	8 (14.5)
	NA	4 (7.3)
Time from diagnosis to pomalidomide treatment (years)	median [range]	2.66 [0.92–7.14]
Median number of treatment line	median [range]	3 [3–7]
>2 prior treatments	*N* (%)	18 (32.7)
Response to prior therapy, *N* (%)	Refractory or Rel/Ref to lenalidomide	49 (89.1)
	Refractory or Rel/Ref to bortezomib	40 (72.7)
	Refractory to both bortezomib and lenalidomide	39 (70.9)
Cause of discontinuation (%)	Total	49 (89.1)
	Disease progression	28 (50.9)
	Withdrawal of consent	9 (16.4)
	Toxicity	5 (9.1)
	Death	7 (12.7)

Abbreviations: β_2MG, β_2 microglobulin; CrCl, Creatinine clearance; ECOG, Eastern Cooperative Oncology Group performance status; Frailty, simplified frailty scale; ISS, international staging system; LDH, lactate dehydrogenase; NA, not assessed; Rel/Ref, relapse and refractory; R-ISS, revised international staging system.

Moreover, patients must exhibit an absolute neutrophil count (ANC) ≥1 × 10^9/L^3 and platelet count ≥50 × 10^9/L (≥30 × 10^9/L if myeloma involvement in the bone marrow was >50%). A washout period of 2 weeks prior to cycle one on day 1 from the prior therapies was required. All the patients provided written informed consent as per institutional guidelines. This study was approved by the institutional review board and was registered at clinicaltrials.gov under National Clinical Trial number NCT03242460 (PORYOU).

2.2 | Treatment and assessment

Patients underwent a 28-day treatment cycle; pomalidomide (4 mg/day on days 1-21, orally) plus dexamethasone (40 mg/day on days 1, 8, 15, and 22, orally). The dose of dexamethasone was reduced to 20 mg/day in patients older than 75 years. Cyclophosphamide (400 mg/day flat dose) was administered orally on days 1, 8, and 15. A first dose reduction of dexamethasone (20 or 10 mg/day on days 1, 8, 15, and 22) was recommended when a minimal response (MR) was achieved 3 months post-PCd therapy initiation and when stable disease (SD) status was achieved 6 months post-PCd initiation. A second dose reduction (10 mg/day dexamethasone or 50 mg/day prednisone on days 1, 8, 15, and 22) was recommended as per the treatment scheme shown in Figure S1. The treatment was continued until progressive disease (PD) status was achieved or when unacceptable toxicity was observed. Pomalidomide was temporarily interrupted for patients with grade ≥ 4 neutropenia, febrile neutropenia, or thrombocytopenia, grade ≥ 3 venous thromboembolism, constipation, peripheral neuropathy, rash, and all other grade ≥ 3 treatment-related adverse events. The dose modifications for cyclophosphamide were at the investigator's discretion, while pomalidomide dose reduction was based on the toxicity grades. Additionally, 100 mg aspirin was administered daily for thromboprophylaxis. The granulocyte colony-stimulating factor was administered to patients with ANC of less than 1 × 10^9/L. Most patients used prophylactic antibiotics (levofloxacin) and anti-viral agents (acyclovir) to prevent infection related complications. The use of bisphosphonates, transfusion support, and other approved supportive strategies was allowed as per routine standard care in each institution.

2.3 | Statistical analysis

The primary endpoint of the study was the median PFS. The secondary endpoints were the overall response rate (ORR), overall survival (OS), and drug toxicities. The PFS and ORR were based on the investigator's assessment of treatment response and PD status in accordance with the IMWG criteria.[16] The number of subjects were calculated using the exponential mean power analysis of the PASS statistical program. This study had 81% power to detect the differences between the null hypothesis median PFS of 4.0 months,[17] and the alternative hypothesis median PFS of 7.5 months in the two-sided test with 5% significance level (alpha). The recruiting number was 49 and the final calculated number was 55 with 10% dropout rate. The patient demographics and the clinical data were analyzed using numerical and graphical epidemiological/statistical methods. Frailty was classified using the simplified frailty scale instead of the IMWG frailty index because this study did not record Activities of Daily Living/Instrumental Activities of Daily Living (ADL/IADL) data.[18,19] The PFS and OS were analyzed using the Kaplan-Meier methodology, and the log-rank test was used for group comparison (univariate analyses). We also conducted multivariate analysis using Cox proportional hazards regression to analyze the independent prognostic impact of the variables on PFS and OS. A *P* value of .05 was considered the limit of significance unless otherwise specified. We used maximally selected log-rank statistics in the maxstat function of the R software (version 3.3.2) to identify the optimal threshold for assessing the survival outcomes of creatinine clearance (CrCl) and beta 2 microglobulin (β2MG). In this study, the optimal thresholds for CrCl and β2MG were 39.8 mL/min and 4.8 mg/L respectively. The results were analyzed using SPSS and R software. The toxicities were

TABLE 2 Multivariate analysis for PFS and OS

Characteristics		N	PFSHR [95% CI]	*P* value	OSHR [95% CI]	*P* value
β_2MG (mg/L)	<4.8	35	1 (Ref.)		1 (Ref.)	
	≥4.8	16	1.10 [0.41-2.90]	.856	0.60 [0.17-2.14]	.426
R-ISS	Stage I	13	1 (Ref.)		1 (Ref.)	
	Stage II	30	0.95 [0.41-2.21]	.902	1.43 [0.44–4.63]	.555
	Stage III	8	2.49 [0.62-9.94]	.197	13.68 [1.76-106.18]	.012
Response to previous lenalidomide treatment	Refractory	11	1 (Ref.)		1 (Ref.)	
	Responsive	44	0.25 [0.09-0.64]	.004	0.58 [0.19-1.79]	0.343
Best response	<VGPR	38	1 (Ref.)		1 (Ref.)	
	≥VGPR	16	0.22 [0.09-0.57]	.002	0.39 [0.12-1.25]	0.115

Abbreviations: β_2MG, β_2 microglobulin; CI, confidence interval; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; ref, reference; R-ISS, revised international staging system; VGPR, very good partial response.

characterized and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events v 4.0.

3 | RESULTS

3.1 | Patient characteristics

The demographic and baseline disease characteristics of 55 patients included in this study are presented in Table 1. The median age of the patients was 73.3 years (range: 64-86 years). Among the patients, eight patients (14.5%) were aged ≥80 years. Among the 55 patients, 24 (32.7%), and 31 (56.4%) patients were classified as nonfrail and frail, respectively. Most of the patients (51 patients) could be categorized according to the risk using the revised international staging system (R-ISS). There were 14 (25.5%) and 8 (14.5%) patients with stage III MM based on ISS and R-ISS, respectively. The median duration from diagnosis to starting PCd therapy was 2.66 years (range: 0.92-7.14 years) and the median number of treatment lines was 3 (range: 3-7). All patients had received prior treatment with lenalidomide and bortezomib (100%). Among the study patients, 40 (72.7%) were refractory or Rel/Ref to bortezomib and 49 (89.1%) were refractory or Rel/Ref to lenalidomide. There were no patients who used other novel agents such as carfilzomib, daratumumab as previous treatment. At the last follow-up, only sixpatients (10.9%) of the total 55 patients underwent treatment. The discontinuation of therapy was due to disease progression, consent withdrawal, toxicities, and death in 50.9, 16.4, 9.1, and 12.7% of the patients, respectively.

3.2 | Efficacy

The ORR and clinical benefit rate (CBR) of PCd therapy were 58.2% and 72.7%, respectively. The responses to PCd therapy based on the investigator's assessment are shown in Table S1. Complete response (CR) was observed in 7.3% of the patients. The median time to the best response was 1.73 months (range 0.89-12.53). The time to the best response in 41 (74.5%), 7 (12.7%), 5 (9.1%) and 1 (1.8%) patients was before 3 months, after 3 months, after 6 months, and after 12 months, respectively. About two-thirds of the patients had ORR according to two prior treatment lines vs greater than two treatment lines (Table S1). The ORR of patient responsive (including Rel/Ref) to prior lenalidomide and bortezomib treatments was 63.6% and 57.7%, respectively. The ORR of

TABLE 3 Summary of the most commonly reported TEAE

Grade TEAE (*N* = 55)	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	All grades
Hematologic adverse events (%)						
Anemia	12 (21.8)	10 (18.2)	5 (9.1)	1 (1.8)	0 (0.0)	28 (50.9)
Neutropenia	10 (18.2)	11 (20.0)	10 (18.2)	1 (1.8)	0 (0.0)	32 (58.2)
Thrombocytopenia	13 (23.6)	11 (20.0)	7 (12.7)	3 (5.5)	0 (0.0)	34 (61.8)
Non-hematologic adverse events (%)						
Constipation	8 (14.5)	7 (12.7)	0 (0)	0 (0)	0 (0)	15 (27.3)
Fatigue	8 (14.5)	3 (5.5)	1 (1.8)	0 (0)	0 (0)	12 (21.8)
Muscle cramp	6 (10.9)	2 (3.6)	4 (7.3)	0 (0)	0 (0)	12 (21.8)
Peripheral neuropathy	8 (14.5)	3 (5.5)	0 (0)	0 (0)	0 (0)	11 (20)
Dyspnea	6 (10.9)	3 (5.5)	1 (1.8)	0 (0)	0 (0)	10 (18.2)
Nausea/anorexia	4 (7.3)	3 (5.5)	1 (1.8)	0 (0)	0 (0)	8 (14.5)
Neurologic disorder	3 (5.5)	2 (3.6)	3 (5.5)	0 (0)	0 (0)	8 (14.5)
Peripheral edema	4 (7.3)	0 (0)	2 (3.6)	0 (0)	0 (0)	6 (10.9)
Insomnia	4 (7.3)	2 (3.6)	0 (0)	0 (0)	0 (0)	6 (10.9)
Skin rash	2 (3.6)	1 (1.8)	1 (1.8)	0 (0)	0 (0)	4 (7.3)
Diarrhea	1 (1.8)	3 (5.5)	0 (0)	0 (0)	0 (0)	4 (7.3)
Kidney injury	1 (1.8)	2 (3.6)	0 (0)	0 (0)	0 (0)	3 (5.5)
Cardiac events	0 (0)	1 (1.8)	1 (1.8)	0 (0)	1 (1.8)	3 (5.4)
Electrolyte imbalance	0 (0)	2 (3.6)	0 (0)	0 (0)	0 (0)	2 (3.6)
DVT and/or PE	1 (1.8)	0 (0)	0 (0)	0 (0)	0 (0)	1 (1.8)
Adverse events of special interest (infection)						
Pneumonia	1 (1.8)	5 (9.1)	7 (12.7)	1 (1.8)	4 (7.3)	18 (32.7)
Sepsis	2 (3.6)	4 (7.3)	1 (1.8)	2 (3.6)	2 (3.6)	11 (20.0)
Febrile neutropenia	0 (0)	0 (0)	7 (12.8)	1 (1.8)	0 (0)	8 (14.5)

Abbreviations: DVT, deep vein thrombosis; LFT, liver function test; PE, pulmonary embolism; TEAE, treatment-emergent adverse event.

patient refractory to prior lenalidomide and bortezomib treatments was 36.4% and 66.7%, respectively. These are described in Table S2. The median follow-up duration of this study was 11.51 months (range; 0.72-37.55 months). The median PFS and median OS for all patients were 6.90 months (95% CI, 4.7-9.0; Figure 1A) and 18.48 months (95% CI, 9.4-27.6; Figure 1B), respectively.

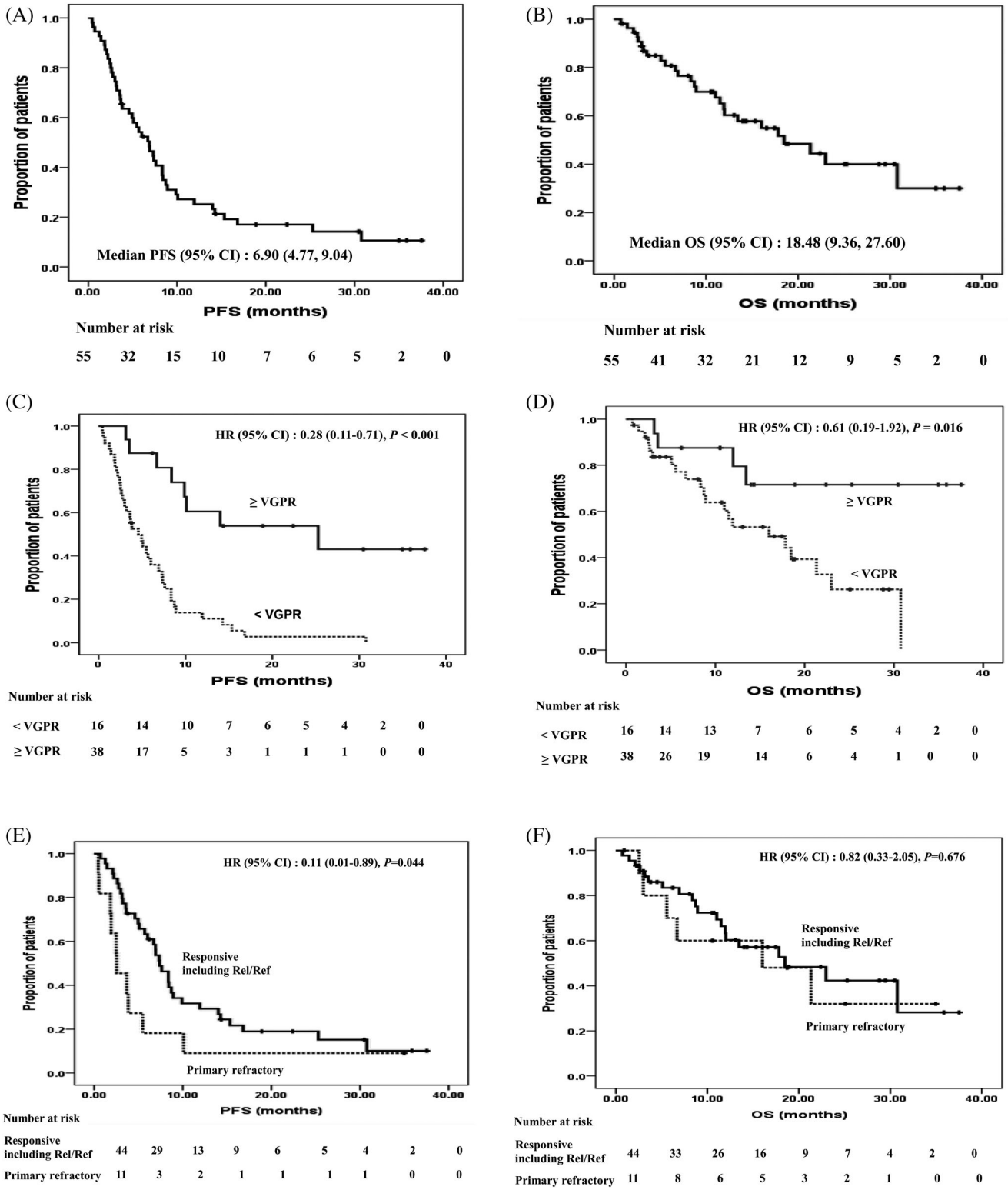

FIGURE 1 Kaplan–Meier analysis of progression-free survival (PFS), A and overall survival (OS), B, of all elderly patients with relapsed and refractory multiple myeloma (RRMM) refractory to both lenalidomide and bortezomib treatments. PFS and OS based on the treatment response, C and D, and prior response to lenalidomide treatment, E and F

3.3 | Risk factors for PFS and OS

The univariate analysis (Table S3) revealed that the median PFS exhibited significant difference based on β2MG levels (<4.8 vs ≥4.8 mg/L; 7.63 vs 3.85 months, *P* = .003, Figure S2C), R-ISS risk (stage I vs II vs III; 8.35 vs 6.94 vs 2.99 months, *P* = .035, Figure S2E), best response (<very good partial response (VGPR) vs ≥VGPR; 4.60 vs 25.28 months, *P* < .001, Figure S1C), and response to previous lenalidomide (primary refractory vs responsive (including Rel/Ref); 2.53 vs 7.36 months, *P* = .044, Figure S1E). The median OS exhibited significant differences based on R-ISS risk (stage I vs II vs III; not-reached [NR] vs 17.85 vs 5.10 months, *P* = .010, Figure S2F), and best response (<VGPR vs ≥VGPR; 16.01 months vs NR, *P* = .016, Figure S1D).The median PFS was not significant based on the number of treatment lines (two treatment lines vs more than two treatment lines; 6.90 vs 6.02 months, *P* = .630, Figure S2A), bortezomib refractory status (primary refractory vs responsive (including Rel/Ref); 3.22 vs 6.90 months, *P* = .613), age (<80 vs ≥80 years; 3.62 vs 6.94 months, *P* = .669), and frailty (nonfrail vs frail; 6.71 vs 7.36 months, *P* = .293).

The multivariate analysis (Table 2) revealed that the independent prognostic factors for PFS included responsiveness to prior lenalidomide treatment (refractory vs responsive [including Rel/Ref]; hazard ratio [HR], 0.25; 95% confidence interval [CI], 0.09-0.64; *P* = .004), and best response (<VGPR vs ≥VGPR; HR, 0.22; 95% CI, 0.09-0.57; *P* = .002). The independent risk factors for OS included R-ISS stage III MM (stage I vs II vs II; HR, 1.43; 95% CI, 0.44-4.63; *P* = .555 vs 13.68; 95% CI, 1.76-106.18; *P* = .012).

3.4 | Adverse events

The treatment-emergent adverse events (TEAEs) are shown in Table 3. The most common grade 3 or 4 hematological adverse events were neutropenia (20.0%), anemia (10.9%), and thrombocytopenia (18.2%). The most common grade 3 or more non-hematological adverse events were pneumonia (21.8%), febrile neutropenia (14.6%) and sepsis (9.0%). The seven deaths recorded during the study period were due to pneumonia (four cases), sepsis (two cases), and cardiac arrest (one case). The incidence rate of deep vein thrombosis was 1.8%. The median time to the initial dose reduction of pomalidomide and cyclophosphamide was 4.5 and 8.1 months, respectively. Pomalidomide treatment was interrupted due to hematological and non-hematological toxicities in 13 and 29 patients, respectively. Additionally, cyclophosphamide treatment was interrupted due to hematological and non-hematological toxicities in 11 and 10 patients, respectively. (Table S4).

4 | DISCUSSION

In this study, transplant-ineligible elderly patients treated with PCd who had failed both lenalidomide and bortezomib treatments showed ORR (58.2%) and PFS and OS (6.9 months and 18.5 months, respectively). Several studies had used PomDex as a salvage regimen for patients with RRMM.[5,17,20] In the MM-003 trial, San Miguel et al,[17] reported the median PFS and OS of 4.0 months and 12.7 months, respectively, and in the STRATUS study, Dimopoulos et al,[20] reported similar results with the median PFS and OS of 4.6 months and 11.9 months, respectively. Baz et al,[5] reported the median PFS and OS of 4.4 months and 16.8 months, respectively in patients treated with PomDex alone, although the dose and treatment schedule was slightly different in these studies.

There are several studies that have evaluated the effect of PCd therapy on patients with RRMM, although these studies used a different dose and interval of cyclophosphamide administration.[5,21-23] Baz et al,[5] reported an ORR and PFS of 65% and 9.5 months, respectively, in 34 patients who were Rel/Ref to multiple lines of treatment including lenalidomide, and underwent PCd therapy (400 mg/day, oral administration of cyclophosphamide on days 1, 8, and 15). Garderet et al,[21] reported higher ORR (85%), PFS rate (2-year PFS, 68.4%), and OS rate (2-year OS, 92.6%) for transplant-eligible patients who underwent PCd therapy with a lower dose of cyclophosphamide (300 mg/day on days 1, 8, 15, and 22) at first relapse after progression on lenalidomide maintenance. Larocca et al,[4] administered pomalidomide at a dose of 1-2.5 mg/day, cyclophosphamide at 50 mg every other day, and prednisone at 50 mg every other day during six treatment cycles for 28 days, followed by pomalidomide prednisone maintenance therapy. The ORR, median PFS, and 1-year OS rate were 51%, 10.4 months, and 69%, respectively. Trudel et al,[23] reported a single-center retrospective study of PCd for RRMM in a real-life setting. A total of 49 patients treated with pomalidomide (4 mg once daily, administered orally on days 1-21 of each 28-day cycle), cyclophosphamide (300 mg/day, administered weekly on days 1, 8, 15, and 22), and dexamethasone (40 mg, administered weekly on days 1, 8, 15, and 22). The ORR was 76%, including 27% very good partial response and the estimated median PFS was 7.3 months. Our study demonstrated that PCd therapy can result in similar response rates and relatively shorter survival outcomes as compared to the previous reported studies.[4,5,21] This could have been due to several factors, including a high number of frail (56.4%) and heavily treated patients who had received more than two lines of prior chemotherapy (32.7%). The independent prognostic factors for PFS were achieving VGPR, and responsiveness (including Rel/Ref) to prior lenalidomide treatment. Previous prospective studies using PCd,[4,5] have reported that the prognostic factors for PFS are the number of prior therapies, β2MG levels, old age, and extent of treatment response. Moreover, Larocca et al demonstrated that the median PFS in patients refractory to lenalidomide was lower than that in patients at relapse. These results concurred with those of this study, especially the extent of response and responsiveness to prior lenalidomide treatment.

In this study, many adverse events were observed, including pneumonia and sepsis. These adverse events and deaths are critical issues in clinical trials and clinical practice. The treatment with pomalidomide results in both hematological (long-term neutropenia) and non-hematological toxicities. The MM003 study and several other studies on PCd have also revealed the high incidence of neutropenia and non-hematological toxicities, including pneumonia and sepsis.[4,5,17,21] Thus,

although the PCd therapy has higher response rates and better survival outcomes, it is associated with frequent and severe toxicities. As this study included many elderly and frail patients as compared to the other PCd studies, old age may have contributed to an increased incidence of infection-related toxicities, including pneumonia and sepsis. Hence, initial dose adjustments and active dose modifications during PCd treatment are important for reducing the toxicities and improving treatment outcomes.

Novel therapeutic agents, such as bortezomib, carfilzomib, daratumumab, isatuximab or elotuzumab are combined with the PomDex combination.[6,7,9-11,24] These drugs have exhibited similar response rates and survival outcomes as compared to the other reported PCd studies, including this study. The ORR of patients undergoing PCd therapy was >50%. Additionally, the patients who underwent PCd therapy exhibited better survival outcomes than the patients who underwent PomDex therapy. However, the cost of these novel therapeutic agents is very high as compared to cyclophosphamide.

In summary, this study has demonstrated that PCd therapy is an effective and a relatively inexpensive strategy for the elderly patients with RRMM who had failed both bortezomib and lenalidomide treatments. The superior survival outcomes of PCd therapy were associated with better treatment response (≥VGPR), and responsiveness to prior lenalidomide treatment (responsive (including Rel/Ref)). However, there were a large proportion of frail patients among elderly patients with MM and relatively high incidence rates of infection in this study. Therefore, early dose modification of cyclophosphamide and pomalidomide with prevention measures for infections should be considered to improve the treatment outcomes and to decrease toxicities.

ACKNOWLEDGMENTS

The authors would like to thank all the researchers and research nurses for their help in data collection. Special thanks to Dr. Xavier Leleu for reviewing this paper. We would like to thank Editage (www.editage.co.kr) for English language editing. The study was supported by the Celgene Corporation.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All authors had access to the primary clinical trial data. This study was planned and conceptualized by Chang-Ki Min and Sung-Soo Yoon. The manuscript was prepared by Ho Sup Lee. The patient information was provided by various investigators at KMMWP. All authors were involved in the manuscript preparation and approved the final version of the manuscript.

ORCID

Ho Sup Lee https://orcid.org/0000-0001-5974-6884
Jin Seok Kim https://orcid.org/0000-0001-8986-8436
Sung-Soo Yoon https://orcid.org/0000-0003-2591-7459

REFERENCES

1. Palumbo A, Facon T, Sonneveld P, et al. Thalidomide for treatment of multiple myeloma: 10 years later. *Blood*. 2008;111(8):3968-3977.
2. Cavo M, Tacchetti P, Patriarca F, et al. Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study. *Lancet*. 2010;376(9758):2075-2085.
3. Lonial S. Relapsed multiple myeloma. *Hematology Am Soc Hematol Educ Program*. 2010;2010(1):303-309.
4. Larocca A, Montefusco V, Bringhen S, et al. Pomalidomide, cyclophosphamide, and prednisone for relapsed/refractory multiple myeloma: a multicenter phase 1/2 open-label study. *Blood*. 2013;122(16):2799-2806.
5. Baz RC, Martin TG, Lin H-Y, et al. Randomized multicenter phase 2 study of pomalidomide, cyclophosphamide, and dexamethasone in relapsed refractory myeloma. *Blood*. 2016;127(21):2561-2568.
6. Chari A, Suvannasankha A, Fay JW, et al. Daratumumab plus pomalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. *Blood*. 2017;130(8):974-981.
7. Paludo J, Mikhael JR, LaPlant BR, et al. Pomalidomide, bortezomib, and dexamethasone for patients with relapsed lenalidomide-refractory multiple myeloma. *Blood*. 2017;130(10):1198-1204.
8. Chim CS, Kumar SK, Orlowski RZ, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. *Leukemia*. 2018;32(2):252-262.
9. Dimopoulos MA, Dytfeld D, Grosicki S, et al. Elotuzumab plus pomalidomide and dexamethasone for multiple myeloma. *N Engl J Med*. 2018;379(19):1811-1822.
10. Shah JJ, Stadtmauer EA, Abonour R, et al. Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma. *Blood*. 2015;126(20):2284-2290.
11. Attal M, Richardson PG, Rajkumar SV, et al. Isatuximab plus pomalidomide and low-dose dexamethasone versus pomalidomide and low-dose dexamethasone in patients with relapsed and refractory multiple myeloma (ICARIA-MM): a randomised, multicentre, open-label, phase 3 study. *Lancet*. 2019;394(10214):2096-2107.
12. Pelligra CG, Parikh K, Guo S, et al. Cost-effectiveness of pomalidomide, carfilzomib, and daratumumab for the treatment of patients with heavily pretreated relapsed–refractory multiple myeloma in the United States. *Clin Ther*. 2017;39(10):1986, e1985-2005.
13. Gong CL, Studdert AL, Liedtke M. Daratumumab vs pomalidomide for the treatment of relapsed/refractory multiple myeloma: a costeffectiveness analysis. *Am J Hematol*. 2019;94(3):E68-E70.
14. Sonneveld P. Management of multiple myeloma in the relapsed/refractory patient. *Hematology Am Soc Hematol Educ Program*. 2017;2017(1):508-517.
15. Sonneveld P, Avet-Loiseau H, Lonial S, et al. Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group. *Blood*. 2016;127(24):2955-2962.
16. Kumar S, Paiva B, Anderson KC, et al. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *Lancet Oncol*. 2016;17(8):e328-e346.
17. Miguel JS, Weisel K, Moreau P, et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2013;14(11):1055-1066.
18. Facon T, Dimopoulos MA, Meuleman N, et al. A simplified frailty scale predicts outcomes in transplant-ineligible patients with newly diagnosed multiple myeloma treated in the FIRST (MM-020) trial. *Leukemia*. 2020;34(1):224–233.

19. Engelhardt M, Dold SM, Ihorst G, et al. Geriatric assessment in multiple myeloma patients: validation of the International Myeloma Working Group (IMWG) score and comparison with other common comorbidity scores. *Haematologica*. 2016;101(9):1110-1119.
20. Dimopoulos MA, Palumbo A, Corradini P, et al. Safety and efficacy of pomalidomide plus low-dose dexamethasone in STRATUS (MM-010): a phase 3b study in refractory multiple myeloma. *Blood*. 2016;128(4):497-503.
21. Garderet L, Kuhnowski F, Berge B, et al. Pomalidomide, cyclophosphamide, and dexamethasone for relapsed multiple myeloma. *Blood*. 2018;132(24):2555-2563.
22. Chen R, Wang Y, Luan C, Gao C, Zhang X, Chen B. Effect of pomalidomide on relapsed/refractory multiple myeloma: a systematic review and meta-analysis. *J Cancer*. 2017;8(10):1801-1808.
23. Trudel S, Tessoulin B, Jullien M, et al. Pomalidomide, cyclophosphamide, and dexamethasone for relapsed/refractory multiple myeloma patients in a real-life setting: a single-center retrospective study. *Ann Hematol*. 2019;98(6):1441-1447.
24. Richardson PG, Hofmeister CC, Raje NS, et al. Pomalidomide, bortezomib and low-dose dexamethasone in lenalidomide-refractory and proteasome inhibitor-exposed myeloma. *Leukemia*. 2017;31(12):2695-2701.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Lee HS, Kim K, Kim SJ, et al. Pomalidomide, cyclophosphamide, and dexamethasone for elderly patients with relapsed and refractory multiple myeloma: A study of the Korean Multiple Myeloma Working Party (KMMWP-164 study). *Am J Hematol*. 2020;95:413–421. https://doi.org/10.1002/ajh.25726