Superior outcomes and high-risk features with carfilzomib, lenalidomide, and dexamethasone combination therapy for patients with relapsed and refractory multiple myeloma: results of the multicenter KMMWP2201 study

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Abstract

Carfilzomib, lenalidomide, and dexamethasone (KRd) combination therapy improves the survival of patients with relapsed and/or refractory multiple myeloma (RRMM). Nonetheless, evidence on the use of KRd in Asian populations remains scarce. Accordingly, this study aimed to investigate this regimen's efficacy in a large group of patients. This retrospective study included patients with RRMM who were treated with KRd at 21 centers between February 2018 and October 2020. Overall,

364 patients were included (median age, 63 years). The overall response rate was 90% in response-evaluable patients, including 69% who achieved a very good partial response or deeper responses. With a median follow-up duration of 34.8 months, the median progression-free survival (PFS) was 23.4 months and overall survival (OS) was 59.5 months. Among adverse factors affecting PFS, high-risk cytogenetics, extramedullary disease, and doubling of monoclonal protein within 2-3 months prior to start of KRd treatment significantly decreased PFS and OS in multivariate analyses. Patients who underwent post-KRd stem cell transplantation (i.e., delayed transplant) showed prolonged PFS and OS. Grade 3 or higher adverse events (AE) were observed in 56% of the patients, and non-fatal or fatal AE that resulted in discontinuation of KRd were reported in 7% and 2% of patients, respectively. Cardiovascular toxicity was comparable to that reported in the ASPIRE study. In summary, KRd was effective in a large, real-world cohort of patients with RRMM with long-term follow-up. These findings may further inform treatment choices in the treatment of patients with RRMM.

Introduction

Antimyeloma therapy has progressed over the last decade with the sequential introduction of second-generation proteasome inhibitors (PI), monoclonal antibodies (mAb), bispecific antibodies (BiTE), and chimeric antigen receptor T-cell therapies.[1-7] Among these, carfilzomib, a second-generation epoxyketone-based irreversible PI, in combination with lenalidomide and dexamethasone, dramatically improved the treatment outcome of relapsed and/or refractory multiple myeloma (RRMM).[1] Its efficacy has been confirmed in the phase III ASPIRE trial, which led to global regulatory approval. Subsequently, prospective clinical trials adopted carfilzomib, lenalidomide, and dexamethasone (KRd) in the upfront setting and it has since been used as the backbone for various combination regimens including mAb for patients with multiple myeloma (MM) with high-risk genetic features as well as for patients with RRMM.[8-11]

Despite the wealth of evidence on the use of the KRd regimen to treat MM, the effectiveness and toxicity of the KRd triplet combination regimen have not been verified in a large real-world population of Asian patients with RRMM; in particular, the ASPIRE trial had poor cross-ethnic generalizability.[12] In addition, a previous phase I Japanese study, which had strict eligibility criteria, and a retrospective Korean study, which included 25% of lenalidomide-refractory patients, showed shorter progression-free survival (PFS) than that showed by the ASPIRE study after a limited duration of follow-up.[13,14] Furthermore, carfilzomib and dexamethasone doublet therapy was associated with an elevated risk of grade 3 or higher adverse events (AE) in an Asian study cohort.[15] However, the efficacy and toxicity of KRd combination therapy in a large cohort of patients with RRMM with long-term follow-up remains to be established. To address this issue, our study aimed to examine the overall effectiveness and adverse event profile of KRd combination therapy in real-world patients with RRMM and further analyze the impact of their clinical characteristics, focusing in particular on high-risk factors that might adversely influence the efficacy of KRd therapy in this setting.

Methods

Retrospective data were collected for 381 patients treated with carfilzomib (Kyprolis®, Amgen Inc.), lenalidomide, and dexamethasone (KRd) combination therapy for RRMM at 21 participating centers for the Korean Multiple Myeloma Working Party (KMMWP) between February 2018 and October 2020. During this study period, KRd was the sole lenalidomide-based triplet therapy reimbursed amongst newer agent combination regimens. Among these patients, 17 were excluded from analysis because of ineligibility for the treatment commencement date and missing information on first-line therapy. The data cutoff date for all patients was March 2023. The primary objective of this study was to evaluate the effectiveness of KRd by examining the overall PFS. Secondary objectives were examining PFS according to high-risk factors, overall survival (OS), overall response rate (ORR), and AE. High-risk factors were defined by the presence of an International Staging System (ISS) stage III, revised ISS (R-ISS) stage III, high-risk cytogenetics at the time of initial diagnosis, extramedullary disease (EMD), symptomatic disease (hypercalcemia, renal failure, anemia, and bone lesions), doubling of the M protein within 2-3 months of KRd therapy, the presence of amyloidosis, and plasma cell leukemia (PCL) at the time of treatment. High-risk cytogenetics were indicated when the results were positive for t(4;14), t(14;16), and del (17p) by G-banding or fluorescence *in situ* hybridization (FISH), based on recommendations from the International Myeloma Working Group (IMWG) consensus panel 2.[16] Demographic data, baseline characteristics of MM, effectiveness, and AE of KRd therapy were obtained by a meticulous review of electronic medical records, according to a protocol approved by the Institutional Review Board (DAUHIRB-22-081) of each participating hospital, in accordance with the Declaration of Helsinki. This study was approved by the Scientific Committee of KMMWP (KMM2201). (For further details see *Online Supplementary Methods*).

Statistical analysis

The baseline characteristics were summarized using descriptive statistics. The ORR was defined as the per-

centage of patients who achieved a partial response (PR) or better.[17] Relative dose intensity (RDI) was calculated as the dose divided by the planned dosage per cycle. Univariate analysis of the binary factors affecting the ORR was conducted using the χ^2 test, and the *P* value was 2-sided. The ORR was illustrated using GraphPad Prism (version 9.4.1; GraphPad Software, San Diego, CA, USA) according to the tested variables. Additionally, PFS was calculated from the first date of KRd administration to the date of disease progression, death, or censoring. Moreover, PFS2 was defined from the date of KRd to the date of myeloma progression on the next-line treatment or death from any cause or censoring. Furthermore, OS was estimated from the first date of KRd to the date of death or censoring. Kaplan-Meier curves were used to analyze PFS, PFS2, and OS, and the differences between variables were compared using the log-rank test. Multivariate survival analysis of PFS and OS were performed using the Cox proportional hazards model. $P<0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 28.0 (IBM Corp. Version 28.0. Armonk, NY, USA) and R 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria)

Results

Patients' baseline characteristics

Baseline patient demographics, disease, and treatment data are shown in Table 1. Three hundred and sixty-four patients were treated with KRd combination therapy for RRMM. Median age was 63 years (range, 28-85 years). Two hundred and thirteen patients (59%) had baseline features that did not meet the eligibility criteria for the ASPIRE trial. *Online Supplementary Figure S1* illustrates the trial-ineligibility in this study, of which the biggest reasons for exclusion was bortezomib refractoriness (33%), followed by creatinine clearance <50 mL/min (23%), platelets <50x10^9/L (6%), and an Eastern Cooperative Group performance status (ECOG PS) of ≥3 (6%). Cytogenetic data were available for 77% of the analyzed patients, of which 98 (27%) had one or more high-risk cytogenetics (18 had any 2 of the 3 high-risk cytogenetics; 2 had all 3 high-risk karyotypes). Extramedullary plasmacytomas were observed in 87 (24%) patients at the time of KRd treatment and included 32 patients (9%) with soft tissue plasmacytomas. The median number of previous lines of therapy was one (range, 1-4), with 4% of the patients having received more than 2 lines of therapy. Two hundred and one (55%) patients had been previously treated with autologous stem cell transplantation (auto-SCT), and 4 patients had received allogeneic stem cell transplantation (allo-SCT). Bortezomib and thalidomide were used in 90% and 66% of patients, respectively, and refractoriness to bortezomib and thalidomide was observed in 33% and 25% of patients, respectively.

Overall response after carfilzomib-lenalidomide-dexamethasone treatment

The median number of treatment cycles was 13 (range, 1-55). A total of 147 patients (40%) were maintained on lenalidomide and dexamethasone or lenalidomide alone after 18 cycles of carfilzomib. The median RDI for carfilzomib, lenalidomide, and dexamethasone were 1.00 (range, 0.05-1.00), 0.82 (range, 0.01-1.00), and 0.77 (range, 0.06-1.00), respectively. Response was evaluable in 97% of the patients, and ORR was observed in 90% of the response-evaluable patients. Additionally, very good partial response (VGPR), complete response (CR), and stringent CR (sCR) were achieved in 24%, 31%, and 6% of the patients, respectively (Table 2). Among the 62 patients who were evaluated for minimal residual disease (MRD) using the EuroFlow standard operation procedure, 36% (22 of 62) were Flow MRD-negative, which accounted for 6% of the responses. A detailed summary of the factors affecting ORR is illustrated in *Online Supplementary Figure S2*. Among the baseline patient- and treatment-related factors, older age (≥65 years, ≥70 years, and ≥75 years), ECOG PS ≥3, creatinine clearance (CCr) ≥50 mL/min, and previous auto-SCT or bortezomib treatment did not decrease ORR; however, platelet count <50x10^9/L, bortezomib-refractoriness, bortezomib response duration <12 months, previous thalidomide treatment, thalidomide refractoriness, and thalidomide response duration <12 months led to a decrease in ORR. High-risk disease-related factors, such as presence of EMD, doubling of M protein within 2-3 months of KRd therapy, symptomatic MM, amyloidosis, and plasma cell leukemia at the time of KRd treatment did not significantly impact the response to KRd therapy, but ISS III (ISS I and II *vs*. III; 92% *vs*. 84%; *P*=0.0306), R-ISS III (R-ISS I and II *vs*. III; 92% *vs*. 78%; *P*=0.0023), and high-risk cytogenetics (standard *vs*. high-risk cytogenetics; 93% *vs*. 80%; *P*=0.0041) significantly decreased ORR.

Survival data and analysis of factors affecting progression-free and overall survival

By the date of analysis, 284 (78%) patients had discontinued treatment. The most common cause of treatment termination was disease refractoriness during KRd treatment (52%), followed by AE (9%), transplantation (7%; 21 auto-SCT and 4 allo-SCT), and death from any cause (4%). After a median follow-up duration of 34.8 months (range, 0.00-61.5 months), PFS was 23.4 months (95% Confidence Interval [CI]: 19.0-26.4 months) and OS was 69.5 months with a 3-year OS of 64.7% (95% CI: 59.8%-70%) (Figure 1A, B). Among the high-risk factors that significantly affected survival as shown by univariate analysis, multivariate analysis showed that high-risk cytogenetics, EMD, and doubling of M protein within 2-3 months of KRd therapy significantly shortened the PFS and OS (standard-risk *vs*. high-risk, *P*=0.0077; no EMD *vs*. presence of EMD, *P*=0.0461; no doubling of M protein within 2-3 months *vs*. doubling of

Table 1. Baseline patients' demographic, disease, and treatment data of the current study and the phase III ASPIRE study.

	Current	ASPIRE
Study design	**Retrospective**	**Phase III**
N of patients	**364**	**396**
Age in years, median (range)	63 (28-85)	66 (38-91)
≥65 years, N (%)	149 (41)	192 (53)
≥75 years, N (%)	26 (7)	-
Male gender, N (%)	205 (56)	207 (58)
ECOG PS, N (%)		
0 or 1	301 (84)	336/354 (95)
2	37 (10)	18/354 (5)
≥3	21 (6)	0
Unknown	5	-
ISS, N (%)	At diagnosis	At study entry
I and II	215 (59)	315 (88)
III	127 (35)	45 (12)
Unknown	22 (6)	0
R-ISS, N (%)	At diagnosis	N/A
I and II	239 (66)	-
III	76 (21)	-
Unknown	49 (13)	-
M-protein type, N (%)		
IgG	201 (55)	-
IgA	72 (20)	-
IgM	1 (0.3)	-
Light chain	64 (18)	-
Other*	24 (7)	-
Unknown	2 (1)	-
Light chain type, N (%)		
Kappa	192 (53)	-
Lambda	154 (42)	-
Negative	11 (3)	-
Unknown	7 (2)	-
Cytogenetic risk by FISH, N (%)		
High risk†	98 (27)	75 (21)
del(17p)	60 (16)	36 (10)
t(4;14)	46 (13)	36 (10)
t(14;16)	14 (4)	N/A
Standard risk	182 (50)	199 (55)
Unknown	84 (23)	86 (24)
ANC, $x10^9$/L, median (range)	2 (0.322-17.5)	-
<$1x10^9$/L, N (%)	16 (4)	0
Platelets, $x10^9$/L, median (range)	158 (16-454)	-
<$50x10^9$/L, N (%)	23 (6)	0
Creatinine clearance, mL/min, median (range)	76.37 (5.98-364.90)	-
≥60 mL/min, N (%)	233 (64)	281 (78)
30 to <60 mL/min, N (%)	77 (21)	74 (21)
<30 mL/min, N (%)	36 (10)	5 (1)
Unknown, N (%)	18 (5)	-
Extramedullary plasmacytoma, N (%)	88 (24)	N/A (at any time)
Paraskeletal	55 (15)	-
Soft tissue	32 (9)	-
Not specified	1 (0.3)	-

Continued on following page.

	Current	ASPIRE
Study design	**Retrospective**	**Phase III**
N of patients	**364**	**396**
Number of prior regimens, median (range)	1 (1-4)	-
1 prior regimen, N (%)	311 (85)	224 (62)
2 prior regimens, N (%)	41 (11)	136 (38)
3 prior regimens, N (%)	10 (3)	-
4 prior regimens, N (%)	2 (1)	-
Prior therapies, N (%)		
Bortezomib	326 (90)	248 (69)
Thalidomide	239 (66)	157 (44)
Lenalidomide	1 (0.3)	44 (12)
Autologous SCT	201 (55)	212 (59)
Allogeneic SCT	4 (1)	-
Refractory to bortezomib, N (%)	120 (33)	4 (1)
Refractory to thalidomide, N (%)	92 (25)	-
Time from diagnosis to KRd treatment in months, median (range)	25.0 (1.1-183.8)	44.2 (3-281)

N: number; ECOG PS: Eastern Cooperative Group Performance Status; ISS: International Staging System; R-ISS: Revised International Staging System; M protein: monoclonal protein; FISH: fluorescence *in situ* hybridization; ANC: absolute neutrophil count; SCT: stem cell transplantation; KRd: carfilzomib, lenalidomide, and dexamethasone; N/A: not available. *8 IgD, 2 IgE, and 14 non-secretory myeloma. †Eighteen double-hit patients with del(17p) and t(4;14) (12 patients), t(4;14) and t(14;16) (6 patients), and 2 triplet-hit patients with del(17p), t(4;14), and t(14;16) were included.

Table 2. Comparison of the effectiveness and efficacy of carfilzomib, lenalidomide, and dexamethasone treatment from the current and the phase III ASPIRE study.

	Current	ASPIRE
N of patients	**364**	**396**
Response evaluable patients, N (%)	354 (97)	-
Flow MRD-negative	22 (6)	-
sCR	23 (6)	9 (2)
CR	113 (31)	42 (12)
VGPR	88 (24)	131 (36)
PR	71 (20)	240 (67)
MR	3 (1)	N/A
SD	15 (4)	40 (11)
PD	19 (5)	-
Not evaluable, N (%)	10 (3)	-
Overall response rate,* ≥PR, N (%)	317/354 (90)	282 (78)
Treatment cycles, median (range)	13 (1-55)	17 (1-34)
Time to response in mths, median (range)	1.9 (0.1-39.6)	1.1
Time to best response in mths, median (range)	3.9 (0.3-39.6)	N/A
Carfilzomib RDI, median (range)	1.00 (0.05-1.00)	-
Lenalidomide RDI, median (range)	0.81 (0.01-1.00)	-
Dexamethasone RDI, median (range)	0.79 (0.06-1.00)	-

Krd: carfilzomib, lenalidomide, and dexamethasone; N: number; MRD: minimal residual disease; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; PR: partial response; MR: minimal response; SD: stable disease; PD: progressive disease; mths: months; RDI: relative dose intensity; N/A: not available. *Overall response rate = (N of patients who achieved PR)/(N of response-evaluable patients) × 100.

M protein within 2-3 months, *P*=0.0257) (Table 3). Salvage chemotherapy was administered to 54% of the patients (*Online Supplementary Table S1*). Patients who received consolidative SCT (first SCT 40% and second SCT 60%) after a median of 6 cycles (range, 2-22) of KRd therapy showed a significantly improved PFS (SCT *vs*. no SCT, *P*=0.0259) and OS (SCT *vs*. no SCT, *P*=0.0005), and salvage chemotherapy with newer target agents showed a prolonged PFS2 after KRd therapy (Figure 2A-D). Clinical trial eligibility significantly affected PFS and OS (*Online Supplementary Figure S3A, B*). Among the baseline patients' characteristics, platelets <50x10^9/L significantly shortened PFS and

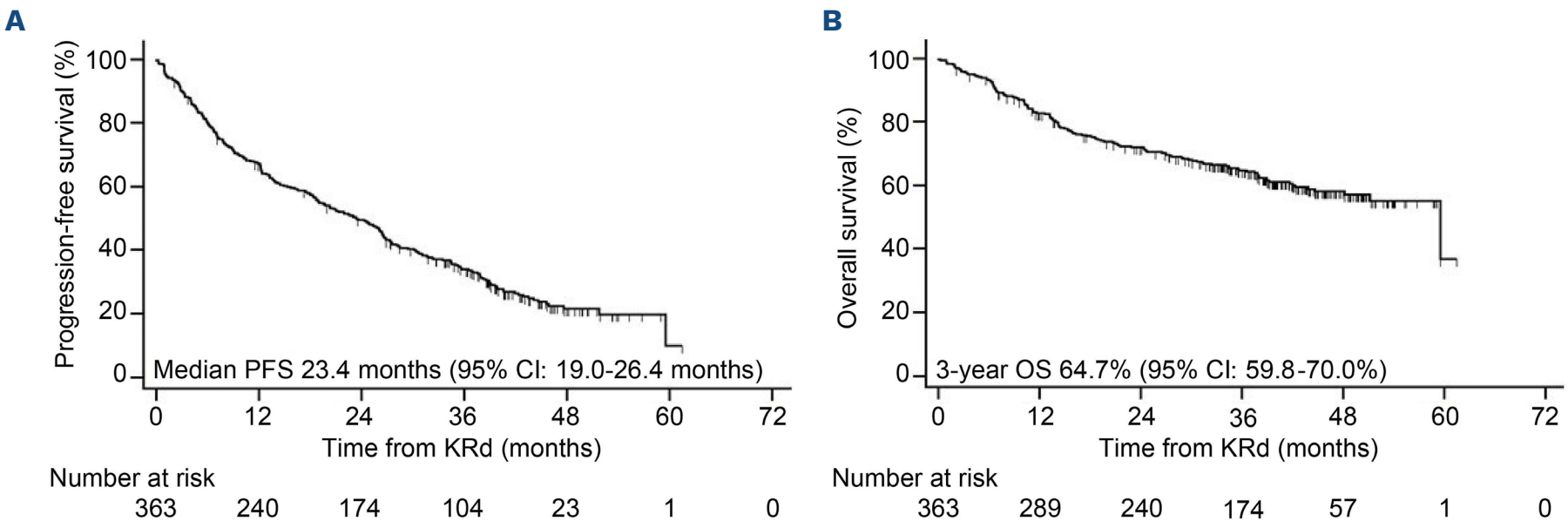


Figure 1. Survival analysis in the total cohort. (A) Progression-free survival (PFS), and (B) overall survival (OS). KRd: carfilzomib, lenalidomide, and dexamethasone.

OS, and patients aged 65 years or older had poorer OS, as shown by multivariate analysis (*Online Supplementary Table S2*). Among the treatment-related factors, a bortezomib response duration >12 months significantly prolonged PFS and OS, as shown by the multivariate analysis (*Online Supplementary Table S3*).

Toxicity profile after carfilzomib-lenalidomide-dexamethasone therapy

A summary of the overall AE profiles of the patients is to be found in Table 4. Of these, 317 patients (87%) experienced AE, of which grade 3 or higher toxicities were observed in 56%. Additionally, AE resulted in dose reductions of carfilzomib, lenalidomide, and dexamethasone in 27%, 38%, and 39% of the patients, respectively, and discontinuation of the drug before the scheduled cycles for carfilzomib in 12% of the patients, and in 12%, and 13% of the patients for lenalidomide and dexamethasone, respectively. Grade 3 or higher cardiovascular AE, such as dyspnea, acute kidney injury, congestive heart failure (CHF), arrhythmias, deep vein thrombosis, hypertension, and ischemic heart disease, were reported in >5% of patients. Secondary primary malignancy (SPM) occurred in 7 patients (2%). Fatal AE occurring during the KRd therapy were reported in 6 patients: 3 cases of secondary malignancies, 2 cases of pneumonia, and one case of ventricular fibrillation associated with CHF (*Online Supplementary Table S4*). Detailed information on the AE reported during or after KRd therapy is provided in *Online Supplementary Table S5*. Neutropenia was the most common grade 3 or higher AE (34%), which resulted in ≥ grade 3 non-fatal neutropenic fever in 3% of the patients. The most common grade 3 or higher non-hematologic AE was infection (12%), followed by fatigue (9%). Ten percent of the patients suffered from acute kidney injury (AKI), especially in patients with significantly lower CCr compared with those who did not experience further AKI after KRd treatment (AKI *vs*. no AKI = mean ± standard deviation, 60.36 ± 22.11 mL/min *vs*. 93.67 ± 66.74 mL/min, respectively, *P*=0.0041) (*Online Supplementary Figure S4*).

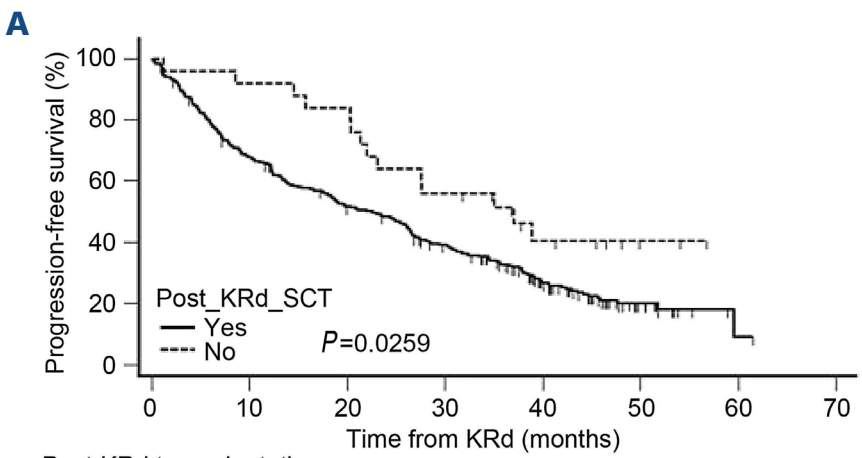
Discussion

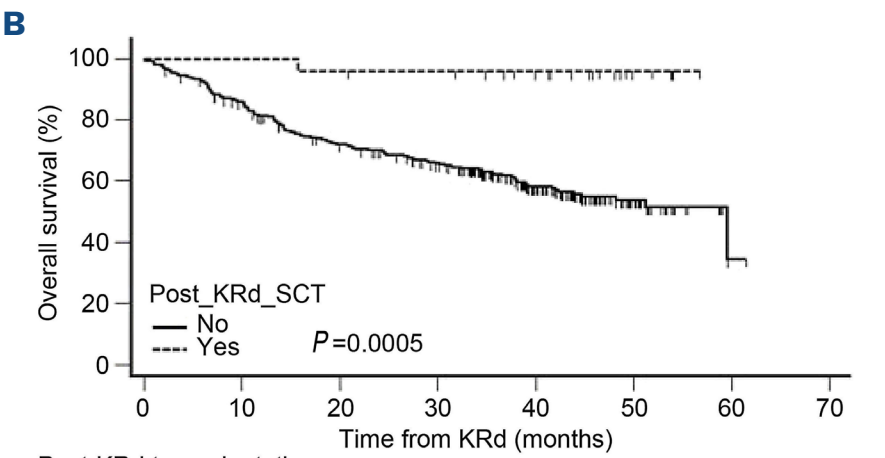
Despite recent advances in novel immunotherapies, triplet combination therapy remains a mainstay of treatment for patients with RRMM globally.[18] The landmark phase III ASPIRE trial examining KRd therapy included only one Asian patient and there is a clear scarcity of data on using KRd therapy in the Asia-Pacific region, thus making a real-world study on KRd conducted in a large cohort of potential importance.[1] This study evaluated 364 Asian patients with RRMM who were treated with the KRd regimen in real-world clinical practice. The ORR was 90%, with a VGPR or higher response of 69%. After a median follow-up of 35 months, the median PFS and OS rates were 23 and 60 months, respectively. Table 5 summarizes the clinical data on KRd therapy, which includes prospective studies and enriches recent retrospective studies in large study populations and Asian cohorts.[1,13,19-22] Although this study included 59% of the patients who were ineligible for the ASPIRE study and those with high-risk cytogenetics and EMD, the PFS and ORR were comparable with and/or better than those of previous prospective and retrospective analyses, with a longer OS than that seen in the pivotal phase III ASPIRE study. There is also a large gap in the data because of the nature and status of government healthcare reimbursement in the Republic of Korea. Specifically, this might have affected the difference between the outcome of this study and that of a previous report of 55 patients who were treated with KRd at their own expense.[14] In the current study, patients were treated in an earlier line of therapy, most patients were lenalidomide-naïve, and had better bone marrow reserve

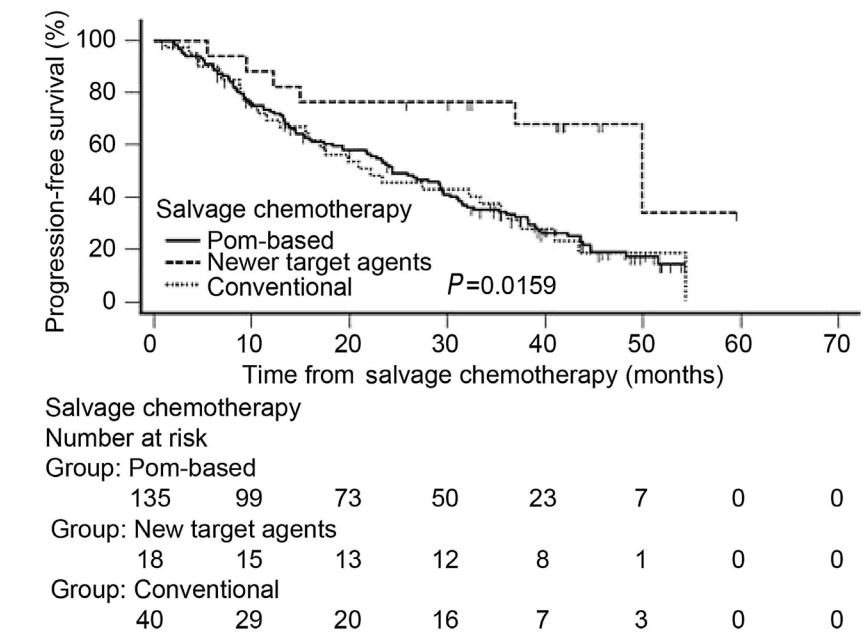
Table 3. Univariate and multivariate analysis of high-risk factors affecting progression-free and overall survival.

		Progression-free survival							Overall survival						
		N	Event	Median PFS in months	Univariate analysis		Multivariate analysis		N	Event	Median OS in months	Univariate analysis		Multivariate analysis	
					HR (95% CI)	*P*	HR (95% CI)	*P*				HR (95% CI)	*P*	HR (95% CI)	*P*
At MM diagnosis															
ISS	I, II	215	154	26.1	-	-	-	-	215	72	-	-	-	-	-
	III	127	93	18.7	1.194 (0.923-1.545)	0.1771	-	-	127	59	41.6	1.628 (1.154-2.299)	0.0056	-	-
R-ISS	I, II	239	169	26.1	-	-	-	-	239	77	-	-	-	-	-
	III	76	57	18.7	1.484 (1.099-2.005)	0.0101	-	-	76	42	26.5	2.323 (1.593-3.389)	<0.0001	-	-
Cytogenetic risk	Standard	182	116	28.5	-	-	-	-	182	57	--	-	-	-	-
	High	98	79	11.4	1.848 (1.387-2.463)	<0.0001	2.267 (1.313-3.914)	0.0033	98	47	39	1.942 (1.319-2.859)	0.0008	2.383 (1.258-4.515)	0.0077
At time of KRd treatment															
Extramedullary disease	No	24	15	38.9	-	-	-	-	24	6	-	-	-	-	-
	Yes	87	70	13.6	2.124 (1.205-3.745)	0.0092	3.641 (1.636-8.102)	0.0015	87	46	35.5	2.547 (1.084-5.983)	0.0319	2.750 (1.018-7.431)	0.0461
Doubling of M protein within 2-3 months	No	291	208	25.4	-	-	-	-	291	106	59.5	-	-	-	-
	Yes	43	34	13.9	1.453 (1.010-2.089)	0.0440	2.992 (1.401-6.390)	0.0046	43	23	37.8	1.807 (1.151-2.839)	0.0102	2.440 (1.114-5.344)	0.0257
Symptomatic MM	No	98	65	32.2	-	-	-	-	98	23	59.5	-	-	-	-
	Yes	266	200	18.9	1.500 (1.133-1.986)	0.0046	-	-	266	116	51.2	2.213 (1.414-3.464)	0.0005	-	-
Amyloidosis	No	357	260	35.3	-	-	-	-	357	136	-	-	-	-	-
	Yes	7	5	23.4	0.707 (0.292-1.713)	0.4423	-	-	7	3	59.5	0.930 (0.296-2.919)	0.9006	-	-
Plasma cell leukemia	No	300	214	23.1	-	-	-	-	300	114	59.5	-	-	-	-
	Yes	3	3	4.8	3.058 (0.974-9.599)	0.0554	-	-	3	3	6.9	6.670 (1.846-16.871)	0.0073	-	-

N: number; HR: hazard ratio; MM: multiple myeloma; ISS: International Staging System; R-ISS: Revised International Staging System; KRd: carfilzomib, lenalidomide, and dexamethasone; M protein: monoclonal protein; CRAB: hypercalcemia, renal failure, anemia, or bone lesions.







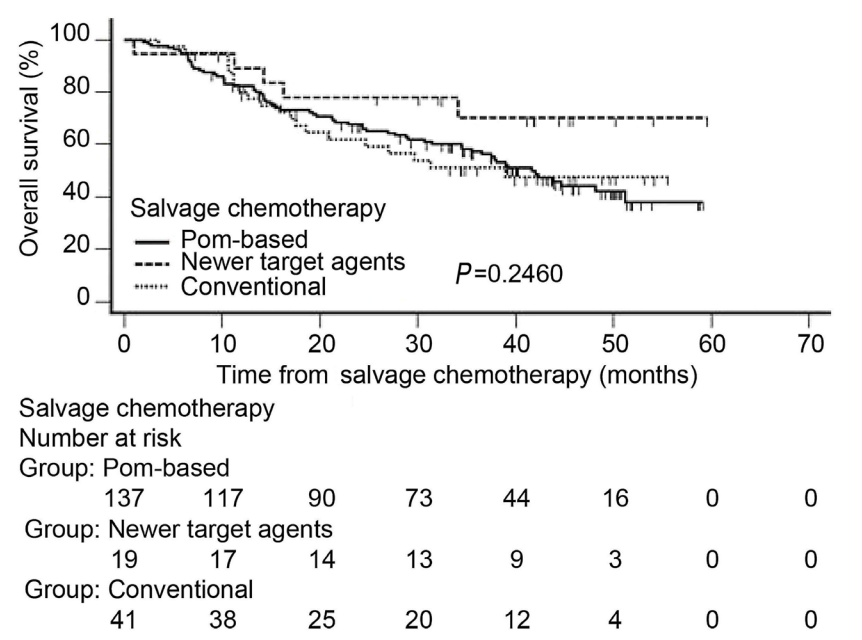


Figure 2. Survival analysis according to post-carfilzomib, lenalidomide and dexamethasone transplantation. (A) Progression-free survival: no *versus* yes = 22.4 months (95% CI: 18.0-26.1) *versus* 37.0 months (95% CI: 22.0-38.9) (*P*=0.0259). (B) 3-year overall survival rate (OS): no *versus* yes = 62.2% (95% CI: 57.1-67.8%) *versus* 100% (95% CI: 100.0-100.0%), *P*=0.0005. Survival analysis according to the salvage chemotherapy in post-carfilzomib, lenalidomide and dexamethasone (KRd) relapse. (C) Progression-free survival2: Pom-based *versus* Newer target *versus* Conventional = 23.3 months (15.9-54.3) *versus* 32.5 months (95% CI: 14.9-59.6), *versus* 19.8 months (95% CI: 12.9-54.4), respectively, *P*=0.2088. (D) 3-year OS rate: Pom-based *versus* Newer target *versus* Conventional = 57.3% (95% CI: 49.3-66.7%) *versus* 70.2% (95% CI: 51.0-96.7%) *versus* 51.1% (95% CI: 37.5-69.7%), respectively, *P*=0.2460. SCT: stem cell transplantation; CI: Confidence Interval; pom: pomalidomide. *Definition of progression-free survival2 = time from the start of KRd therapy to the date of progression after post-KRd salvage chemotherapy. **Category of salvage chemotherapy. Conventional: alkylator-, thalidomide-, bortezomib- and ixazomib-based regimen; Pom-based: pomalidomide / dexamethasone, pomalidomide / cyclophosphamide / dexamethasone, and carfilzomib / pomalidomide / dexamethasone; Newer target agents: daratumumab-, belantamab-, teclistamab-, elranatamab-, and venetoclax-based chemotherapy.

than that of patients who were treated with carfilzomib in combination with lenalidomide-dexamethasone (Rd) as one of the last treatment options. This difference indicates that using effective therapeutic options as an earlier line of therapy favorably affects overall outcome, which is especially influenced by treatment cost in real-world clinical practice and across global healthcare systems.

Notably, this study focused on the performance of KRd therapy according to the aggressiveness of the disease, presence of EMD, doubling of M protein within 2-3 months, symptomatic MM, plasma cell leukemia, and presence of amyloidosis at the time of relapse or refractoriness, as well as ISS, R-ISS, and high-risk cytogenetics at diagnosis of MM, which were included in 24%, 12%, 73%, 2%, 1%, 35%, 21%, and 27% of the patients, respectively. Multivariate analysis revealed that high-risk cytogenetics, the presence of EMD, and doubling of M protein levels within 2-3 months significantly affected PFS and OS. The poor prognostic impact of high-risk cytogenetics is consistent with previous single-arm KRd studies.[19,20] EMD at disease relapse has traditionally been an uncontrollable situation in RRMM as per previous reports, which showed PFS of approximately 4-8 months

and OS of approximately 12 months.[22,23] Although EMD was a poor prognostic factor in this study, ORR was 83% with a PFS of 14 months and OS of 36 months. Recently, bispecific antibody therapies with different targets have shown promising results, with an ORR of 83% in patients with EMD.[24] Hence, it can be inferred that a new combination therapy, especially one involving bispecific antibody therapies with KRd or similar as primary therapy, might be promising for treating patients with EMD. In terms of the doubling of the M protein within 2-3 months at the time of relapse, ORR was 81%, and PFS and OS were 14 and 38 months, respectively. This change in the M protein has been suggested to be a high-risk factor but has not been studied in a large cohort of patients in the era of new agents.[25] To the best of our knowledge, this is the first study to show that a rapid increase in M protein levels is an aggressive tumor-related factor in patients with RRMM treated with Rd-based triplet combination therapy. This also suggests that this clinical feature requires further investigation and additional studies into novel next-generation therapy.

Prior therapies and the quality of response to previous treatments significantly affected the response to KRd therapy, among which a bortezomib response duration longer than 12 months was the sole factor that had a significant impact on longer PFS and OS in multivariate analysis. The outcome of KRd therapy according to prior bortezomib refractoriness has been controversial across prospective and retrospective studies,[14,19,22] which may have been affected by the limited number of patients included. Although we could not make a formal comparison with other Rd-based triplet regimens because of the different characteristics of the patients studied, we suggest that the KRd regimen has the greatest benefit in patients who have a bortezomib response duration that is longer than 12 months; additionally, there may be a limited impact of thalidomide-refractoriness or response duration to thalidomide on the effectiveness of KRd treatment, recognizing that thalidomide use has diminished considerably with lenalidomide now being used as part of upfront therapy and maintenance across most health care jurisdictions.[26-28]

Approximately 6% of the patients could be consolidated with high-dose chemotherapy with stem cell rescue, either in

Table 4. Adverse event profile of the carfilzomib, lenalidomide and dexamethasone combination chemotherapy in real-world practice in the current study compared with the ASPIRE study.

	Current study, N=364		ASPIRE study, N=396	
Median follow-up in months	35		67	
Any AE, N (%)	317 (87)		57 (100)	
Any grade ≥3 AE, N (%)	203 (56)		N/A (84)	
Any SAE, N (%)	-		19 (33)	
AE resulting in dose reduction, N (%)	-		12 (21)	
Carfilzomib	98 (27)		7 (2)	
Lenalidomide	137 (38)		7 (12)	
Dexamethasone	141 (39)		5 (9)	
AE resulting in discontinuation of any drug, N (%)	-		8 (14)	
Carfilzomib	44 (12)		-	
Lenalidomide	44 (12)		-	
Dexamethasone	46 (13)		-	
AE resulting in discontinuation of KRd therapy, N (%)	31 (9)		60 (15)	
Death due to AE, N (%)	6 (2)		6 (2)	
	All grades	**Grade ≥3 AE**	**All grades**	**Grade ≥3 AE**
Adverse events of interest, N (%)				
Dyspnea	54 (15)	14 (4)	76 (19)	11 (3)
Hypertension	12 (3)	2 (1)	56 (14)	17 (4)
Cardiac failure	11 (3)	5 (1)	25 (6)	15 (4)
Ischemic heart disease	3 (1)	1 (0)	23 (6)	13 (3)
Acute kidney injury	35 (10)	6 (2)	33 (8)	13 (3)
Arrhythmias	6 (2)	3 (1)	-	-
Deep vein thrombosis	12 (3)	2 (1)	23 (7)	7 (2)
New primary malignancy, N (%)	8 (2)	-	-	-
Treatment stopped due to AE*, N (%)	31 (9)	-	60 (15)	-
Death due to AE, N (%)	6 (2)	-	6 (2)	-

AE: adverse event; SAE: severe adverse event; N: number; N/A: not available; KRd: carfilzomib, lenalidomide, and dexamethasone. *Detailed information available in *Online Supplementary Table S4*.

Table 5. Comparison of the baseline characteristics and the effectiveness or efficacy of the carfilzomib, lenalidomide and dexamethasone studies.

	Current	Korea[14]	Tuscan[20]	Italy[21]	Europe Israel[22]	Japan[23]	ASPIRE[1]
Study design	Retro	Retro	Prospective observational	Retro	Prospective observational	Prospective observational	Phase III
N of patients	364	55	85	600	383	31	396
Age >65 years, %	37	36	N/A (>75 years, 6)	48	N/A (median, 65 years)	N/A (median, 67 years)	47
ECOG PS ≥3, %	6	9	-	N/A	N/A (ECOG PS 2-4, 15)	6	0
Trial-ineligibility,* %	59	N/A	N/A	N/A	N/A (Frail, 28)	N/A	0
Prev. lines of therapy, median (range)	1 (1-4)	2 (1-5)	1-2	2 (1-11)	1 (1-2)	1 (1-4)	2 (1-3)
High-risk cytogenetics, %	27	31	26	25	15	23	12
EMD, %	24	N/A	4	N/A	N/A	N/A	N/A
Doubling of M protein within 2-3 months, %	12	N/A	N/A	N/A	N/A	N/A	N/A
CrCl <30 mL/min, %	10	9	7	8	N/A	N/A (3, Cr ≥2mg/dL)	0
Len-refractory, %	0.3	25	6	14	57	32	0
Prior ASCT, %	55	55	60	45	64	N/A	56
ORR, % ≥VGPR, %	90 69	73 35	95 57	73 54	84 67	81 52	87 70
Median follow-up duration in mths	35	14	40	16	18	28	67
Median PFS in mths	23	9	36	22	N/A	2-year, 59%	26
Median OS in mths	60	22	5-year, 73%	35	N/A	2-year, 80%	48

KRd: carfilzomib-lenalidomide-dexamethasone; Retro: retrospective; N: number; ECOG PS: Eastern Cooperative Group Performance Status; Prev: previous; EMD: extramedullary disease; M protein: monoclonal protein; CrCl: creatinine clearance; Len: lenalidomide; ASCT: autologous stem cell transplantation; ORR: overall response rate; VGPR: very good partial response; PFS: progression-free survival; OS: overall survival; mths: months; N/A: not available; NR: not reached. *Trial ineligibility is summarized in *Online Supplementary Figure S1*.

their first or second transplantation after a median 6 cycles of KRd treatment, which significantly prolonged PFS and OS. This result is in line with findings from previous retrospective studies that have evaluated the effect of auto-SCT after the salvage KRd regimen either as a first or second auto-SCT, and suggested a potential beneficial effect of consolidative auto-SCT in available patients; however, the number of patients in our study is relatively small, so this has to be interpreted with caution.[29,30] In terms of salvage treatments affecting PFS2, the incorporation of mAb or new classes of drugs into the next line of therapy has been more effective than conventional agents or pomalidomide-based combination therapies without newer agents in this study. Based on these results, the recent development of immunotherapies and their combination regimens may significantly benefit patients who progress after KRd therapy and, in a broad sense, those who are lenalidomide-refractory. Importantly, the use of pomalidomide-based therapy in early relapse has become increasingly established, with pomalidomide combination strategies incorporating dexamethasone, PI and mAb showing substantial efficacy, and obtaining various regulatory approvals accordingly.[31-34] Nonetheless, access to pomalidomide in combination with newer agents remains constrained in many countries globally, making our findings of continued relevance.

Overall, there were no unexpected AE in this large real-world cohort of patients with RRMM. Most of the patients receiving the KRd regiment experienced toxicities; grade 3 or higher AE were reported in 56% of the study population. The incidence of grade 3 or higher AE was lower in comparison with the ASPIRE study possibly due to active dose reductions and use of KRd in an earlier line of therapy for the vast majority of patients. Fatal AE did not increase compared to those in the phase III trial. Hematologic AE were more common than non-hematologic AE and were mostly manageable. Infections were observed in 21% of the patients, but grade 3 or higher infections occurred in 11% of the patients, which led to death in 2 patients. A previous retrospective Korean study on KRd before imbursement has reported a high rate of ≥ grade 3 infections (20%). The reduced incidence of severe infections in this study might reflect the adoption of the KRd regimen as an earlier line of therapy using more cautious monitoring and prophylaxis for infectious complications than those used in the previous report. The slightly higher incidence of AKI in this study than that in the ASPIRE trial is in line with findings from previous studies.[14,35] Patients

who experienced AKI in this study had a lower mean CCr than those who did not experience AKI, which suggests that physicians should be alerted to the possible risks of choosing a carfilzomib-based regimen for treating RRMM patients with renal failure. Although this study included patients with ongoing cardiovascular risk factors, there was no increase in grade 3 or higher cardiovascular AE compared to the pivotal phase III trial ASPIRE. During KRd treatment, 7 patients (2%) had secondary primary SPM, none of whom had related pre-existing cancers. The mechanism of SPM in MM is complex and precise mechanisms continue to be evaluated,[28,36] but there was no correlation between previous alkylator exposure or transplantation and SPM evolution in this study, although the numbers are small, limiting any meaningful interpretation. To the best of our knowledge, this is the first study to analyze the detailed toxicity data of KRd in such a large real-world population with RRMM, which confirmed a tolerability profile comparable to that of previous studies.

In conclusion, the use of carfilzomib in combination with lenalidomide and dexamethasone proved effective with an expected, manageable safety profile when treating a large population of Asian patients with RRMM. Factors reflecting aggressiveness of disease, such as high-risk cytogenetics at diagnosis of MM, EMD, and doubling of the M protein within 2-3 months of relapse and/or refractory status, were associated with decreased PFS and OS in patients treated with KRd therapy. Taken together, these findings may inform future therapeutic advances and direct treatment choices in the management of patients with RRMM. Additionally, our study also confirms that patients with RRMM and both high-risk laboratory and clinical features require further investigation with novel therapeutics to improve outcome.

Disclosures

No conflicts of interest to disclose.

Contributions

JHyL and S-HK designed the study. JHyL, CKM, S-SP, J-CJ, YJL, JSK, H-SU, JHJ, JHM, HJC, M-WL, S-SY, JMB, JHoL, J-JL, S-HJ, H-JS, DYK, JHY, S-SL, YRD, DHY, HC, WSL, HSL, JU, HJK, HRJ, S-HK and KK are responsible for patient enrollment and data collection. JHyL and JC analyzed the data. JHyL, S-HK and KK wrote the paper. All authors revised the paper.

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Data-sharing statement

For original data, please contact Ji Hyun Lee: hidrleejh@dau.ac.kr.

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