Clinical Outcomes of Carfilzomib-based Chemotherapy by Relative Dose Intensity in Patients with Relapsed or Refractory Multiple Myeloma

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INTRODUCTION

Multiple myeloma is a hematologic disorder characterized by abnormal proliferation of plasma cells in the bone marrow. The National Comprehensive Cancer Network guidelines version 1.2024 recommend carfilzomib, lenalidomide, and dexamethasone combination therapy (KRd) as the standard treatment for relapsed or refractory multiple myeloma. For patients with compromised overall performance or frailty, a two-drug regimen with carfilzomib and dexamethasone (Kd) is suggested, along with dose adjustments based on activity level and age.

In the treatment of multiple myeloma, which accounts for the majority of elderly patients, weakness and poor activity performance are generally known to increase the frequency of severe side effects in patients, and in practice, dose reductions are frequent due to adverse drug reactions during anticancer therapy for multiple myeloma.

OBJECTIVES

This study evaluated the dosage intensity of carfilzomib-based therapy, its therapeutic effects, and safety in a retrospective cohort of patients treated at Bundang Seoul National University Hospital from May 1, 2017, to November 30, 2022.

METHODS & MATERIALS

The study included patients aged 19 and above with relapsed or refractory multiple myeloma.

The dose intensity of carfilzomib-based therapy was analyzed by stratifying the relative dose intensity (RDI) for up to 2 cycles.

$$\text{Relative dose intensity(RDI)} = \frac{\text{Actual dose intensity}}{\text{Standartd dose intensity}}$$

$$\text{RDI}_{\text{KRD}} = \frac{\text{RDI}_{\text{K}}+\text{RDIR}+\text{RDID}}{3}\,(1\sim18\text{ cycles}) + \frac{\text{RDI}_{\text{K}}+\text{RDID}}{2}\,(\text{after 18cycles})$$

$$\text{RDI}_{\text{KD}} = \frac{\text{RDI}_{\text{K}}+\text{RDIR}}{2}$$

Treatment outcomes, including overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), were assessed. Multivariate Cox proportional hazard models were employed to analyze factors influencing survival. Variables with p <0.1 in the univariate analysis were added to the multivariate analysis, and the stepwise regression method was used to select the model with the minimum Akaike information criterion (AIC) by repeating the forward selection and backward elimination method at each step.

Safety analysis identified adverse events using the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

For all statistical analysis results, p<0.05 was considered significant.

All statistical analyzes were performed using R version 4.3.2 and R studio version 2023.09.1+494.

RESULTS

The study included 126 eligible patients, with 85 in the KRd group and 41 in the Kd group. The median follow-up duration was 18.7 months (range 0.3-63.2).
The relative dose intensity (RDI) was 0.85±0.15 for the KRd group and 0.66±0.22 for the Kd group. The KRd group showed an ORR of 88.0%, a median PFS of 16.8 months (95% CI 13.6-26.5), and an OS of 33.1 months (95% CI 27.4-43.2). The Kd group exhibited an ORR of 57.9%, a median PFS of 6.4 months (95% CI 3.0-9.8), and an OS of 26.4 months (95% CI 11.5-39.8).

Table 1. Baseline Demographic and Clinical Characteristics

	All (n=126)	KRd (n=85)	Kd (n=41)
Male, n (%)	79 (62.7)	51 (60.0)	28 (68.3)
Age, year, median (range)	65 (40-87)	63 (40-84)	75 (48-87)
CrCl, mean	74.0±28	79.8±25	62.1±30
Comorbidity†, n (%)	79 (62.7)	46 (54.1)	33 (80.5)
Coronary artery disease	21 (16.7)	11 (12.9)	10 (24.4)
Type of M protein, n (%)			
IgG	68 (54.0)	49 (57.6)	19 (46.3)
IgA	20 (15.9)	10 (11.8)	10 (24.4)
IgM	2 (1.6)	2 (2.4)	0 (0.0)
Non-secretory	36 (28.6)	24 (28.2)	12 (29.3)
Light-chain subtype, n (%)			
Kappa	72 (57.1)	50 (58.8)	22 (53.7)
Lambda	53 (42.1)	34 (40.0)	19 (46.3)
Unknown	1 (0.8)	1 (1.2)	0 (0.0)
R-ISS stage, n (%)			
I or II	91 (72.2)	67 (78.8)	24 (58.5)
III	27 (21.4)	17 (20.0)	10 (24.4)
Unknown	8 (6.3)	1 (1.2)	7 (17.1)
Cytogenetic abnormalities‡ by FISH, n (%)			
Standard risk	58 (46.0)	45 (52.9)	13 (31.7)
High risk	31 (24.6)	23 (27.1)	8 (19.5)
Unknown	37 (29.4)	17 (20.0)	20 (48.8)
Previous lines of therapy, n (%)			
1-2 regimens	111 (88.1)	84 (98.8)	27 (65.6)
≥3 regimens	15 (11.9)	1 (1.2)	14 (34.1)
Prior therapy, n (%)			
Bortezomib	121 (96.0)	82 (96.5)	39 (95.1)
Lenalidomide	39 (31.0)	2 (2.4)	37 (90.2)
Autologous transplant	57 (45.2)	49 (57.6)	8 (19.5)
Reason for treatment with KRd/Kd			
Biochemical relapse	92 (73.0)	66 (77.6)	26 (63.4)
Symptomatic relapse	18 (14.3)	13 (15.3)	5 (12.2)
Refractory	16 (12.7)	6 (7.1)	10 (24.3)

CrCl, Creatinine clearance; R-ISS, Revised International Staging System; FISH, fluorescence in situ hybridization
†Diabetes mellitus, cardiovascular disease, chronic kidney disease
‡Cytogenetic abnormalities: t(14;16), gain/amp(1q21), and del(17p)

RESULTS

Table 2. Relative Dose Intensity

	KRd (n=80)	Kd (n=33)
First 2 cycles (RDI_{2cycle})	0.85±0.13	0.66±0.22
Carfilzomib-RDI (RDI_K)	0.87±0.16	0.64±0.19
Lenalidomide-RDI (RDI_R)	0.82±0.20	-
Dexamethasone-RDI (RDI_D)	0.85±0.18	0.68±0.40
Total treatment period (RDI_{total})	0.73±0.15	0.62±0.17

Table 3. Best Response and Overall Response Rate (n, %)

Best response	KRd (n=83)	Kd (n=38)
Complete response (CR)	1 (1.2)	0 (0.0)
Very good partial response (VGPR)	49 (59.0)	9 (23.7)
Partial response (PR)	23 (27.7)	13 (34.2)
Minimal response (MR)	6 (7.2)	10 (26.4)
Progressive disease (PD)	4 (4.8)	6 (15.8)
Overall response rate (ORR)	**88.0%**	**57.9%**

Figure 1. Treatment Response according to RDI_K: PFS

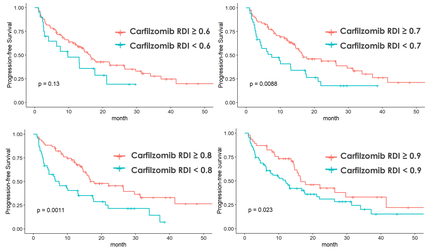
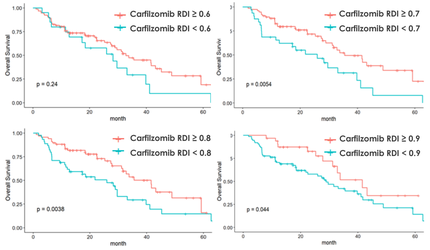


Figure 2. Treatment Response according to RDI_K: OS



RESULTS

Table 4. Univariate and Multivariate Analysis of Progression-free Survival

Variables		Univariate HR (95% CI)	Univariate P-value	Multivariate HR (95% CI)	Multivariate P-value
Gender	Female	1			
	Male	1.36 (0.82-2.26)	0.237		
Age	<70	1			
	≥70	1.40 (0.85-2.29)	0.182		
R-ISS stage	I or II	1		1	
	III	3.16 (1.80-5.55)	<0.001	4.11 (2.24-7.54)	<0.001*
Auto PBSCT history	Yes	1		1	
	No	1.66 (1.02-2.71)	0.044	1.52 (0.87-2.68)	0.142
Previous lines of therapy	1-2	1		1	
	≥3	2.56 (1.41-4.65)	0.002	2.53 (2.24-7.54)	0.006*
RDI_K	≥0.7	1		1	
	<0.7	2.21 (1.36-3.59)	0.001	2.00 (1.09-3.65)	0.025*

HR, Hazard ratio; R-ISS, Revised International Staging System

Table 5. Univariate and Multivariate Analysis of Overall Survival

Variables		Univariate HR (95% CI)	Univariate P-value	Multivariate HR (95% CI)	Multivariate P-value
Age	<70	1			
	≥70	1.61 (0.96-2.70)	0.071		
CAD	No	1		1	
	Yes	2.29 (1.14-4.61)	0.020	1.93 (0.92-4.06)	0.082
Type of M protein	IgG	1		1	
	Non-IgG	1.79 (1.06-3.03)	0.028	2.19 (1.22-3.94)	0.009*
Light-chain subtype	Kappa	1			
	Lambda	1.73 (1.02-2.91)	0.040		
R-ISS stage	I or II	1		1	
	III	2.20 (1.19-4.09)	0.012	2.57 (1.28-5.18)	0.008*
Cytogenetic abnormalities‡	Standard risk	1		1	
	High risk	1.88 (1.05-3.37)	0.034	2.20 (1.16-4.17)	0.016*
Auto PBSCT history	Yes	1			
	No	2.10 (1.22-3.59)	0.007	2.23 (1.24-4.12)	0.007*
RDI_K	≥0.7	1		1	
	<0.7	1.96 (1.17-3.27)	0.010	1.40 (0.75-2.60)	0.290

HR, Hazard ratio; CAD, Coronary artery disease; R-ISS, Revised International Staging System; AutoPBSCT, Autologous peripheral blood stem cell transplantation
‡Cytogenetic abnormalities: t(14;16), gain/amp(1q21), and del(17p)

As a result of multivariate analysis, PFS was found to be reduced when RDI was less than 0.7, R-ISS stage III and ≥3 chemotherapy were previously administered. OS was confirmed to be reduced significantly in non-IgG type M protein, R-ISS stage III, cytogenetic/FISH high risk, non-Auto PBSCT history.

RESULTS

Adverse reactions were reported in 124 (98.4%) of all patients. Cytopenia and infection were frequent in both groups, and rash and peripheral neuropathy were more common in the KRd group. Grade 3 or higher side effects occurred in 62 patients (72.9%) in the KRd group and 30 patients (73.2%) in the Kd group.

Patients who had dose reductions and administration schedule changes were 57.1% and 68.2%, respectively, in the KRd group, and 61% and 73.2% of patients in the Kd group had reductions or discontinuations. The main reasons were hematological adverse reactions, infection, fatigue, loss of appetite, and peripheral neuropathy in the KRd group, and hematological adverse reactions, infection, fatigue, and cardiovascular adverse reactions such as dyspnea in the Kd group.

CONCLUSIONS

In conclusion, the study found that an carfilzomib RDI of 0.7 or less in carfilzomib-based therapy up to two cycles impacted PFS. Patients experience a variety of adverse reactions in the first two cycles of treatment, including severe adverse reactions, and as adverse reactions repeat, the RDI decreases.

Therefore, appropriate supportive care and adverse reaction monitoring should be provided to ensure optimal treatment.

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