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Carfilzomib prescribing patterns and outcomes for relapsed or refractory multiple myeloma: a real-world analysis

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Despite the widespread use of carfilzomib (K) in relapsed/refractory multiple myeloma (RRMM), there is no consensus on optimal K dose in milligrams per square meter (mg/m2) or dosing schedule. We assessed three modern K prescribing patterns in RRMM using a large United States electronic health record-derived database. Our final cohort ($n = 486$) included 136 patients (28.0%) who received K 56 mg/m2 once weekly (K56-1x), 86 (17.7%) who received 56 mg/m2 twice weekly (K56-2x), and 264 (54.3%) who received 70 mg/m2 once weekly (K70-1x). Between 2016 and 2023, once-weekly dosing became more common: K70-1x proportions changed from 21.1% in 2016 to 50.6% in 2023, K56-1x from 15.8% to 37.0%, and K56-2x from 63.2% to 12.3%. Median progression-free survival was 13.0 months [95% confidence interval (CI) 11.2-20.7] for K56-1x, 13.2 months (95% CI 9.0-28.1 months) for K56-2x, and 10.9 months (95% CI 9.9-15.3 months) for K70-1x; these differences were not statistically significant (log-rank $p = 0.46$). Rates of heart failure was comparable (<5% in all cohorts). In summary, our findings do not support improved outcomes with twice-weekly carfilzomib in RRMM. K56-1x may provide the best balance of efficacy, safety, and avoidance of time toxicity from frequent infusions.

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INTRODUCTION

Multiple myeloma (MM) is a hematologic malignancy characterized by the clonal proliferation of plasma cells and accompanying production of abnormal monoclonal proteins. Proteasome inhibitors (PIs) such as bortezomib or carfilzomib are commonly used to treat newly diagnosed MM and relapsed/refractory MM (RRMM), usually in combination with dexamethasone and other classes of agents. Bortezomib was the first PI approved for RRMM based on superior outcomes, including both progression-free survival (PFS) and overall survival (OS), compared to high-dose dexamethasone alone [1]. Carfilzomib was developed soon afterward, with preclinical data demonstrating more selective and irreversible proteasome binding that leads to sustained inhibition and tumor cell death [2–4]. Clinical studies of intravenous carfilzomib demonstrated less neuropathy than with bortezomib, although cardiac and renal toxicities were noted [5]. In the randomized ENDEAVOR trial of either PI in combination with dexamethasone in RRMM, carfilzomib plus dexamethasone was shown to improve PFS and OS versus bortezomib plus dexamethasone [6, 7]. As a result, carfilzomib has become a commonly used PI in RRMM trials such as ASPIRE, CANDOR, IKEMA, and SELECT [8–11].

Over the years, carfilzomib dosing has varied significantly between trials in RRMM (Supplementary Table 1). During initial phase I studies (PX-171-00125 and PX-171-00226), two carfilzomib dosing schedules were used: 5 consecutive days on a 14-day cycle or 2 consecutive days per week for 3 weeks during a 28-day cycle. A maximum tolerated dose was not established, and an initial dose of 20 milligrams per meter squared (mg/m^2) with subsequent escalation to 27 mg/m^2 was chosen based on the observed side effect profile [12, 13]. Subsequent trials have utilized many different dosing patterns for carfilzomib including 36 mg/m^2, 56 mg/m^2, and 70 mg/m^2 after the initial dose(s) of 20 mg/m^2. Similarly, both once-weekly and twice-weekly (on two consecutive days per week) carfilzomib dosing schedules have been used in subsequent trials.

Carfilzomib 56 mg/m^2 twice weekly (K56-2x) has been used in several Phase 3 RRMM studies including ENDEAVOR, CANDOR, and IKEMA [6, 9, 10]. However, the randomized Phase 2 SWOG S1304 study compared K56-2x versus 27 mg/m^2 twice-weekly (K27-2x) in RRMM but found no difference in progression-free survival (PFS) or overall survival (OS) between the strategies [14]. In contrast, the randomized Phase 3 ARROW trial found that carfilzomib 70 mg/m2 once-weekly (K70-1x) was associated with improved PFS and a similar safety profile compared to K27-2x [15]. Importantly, both SWOG S1304 and ARROW used carfilzomib-dexamethasone (Kd) doublet therapy without CD38 monoclonal antibodies (mAbs) such as daratumumab or isatuximab or immunomodulatory drugs (IMiDs) such as lenalidomide or

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pomalidomide. Carfilzomib 56 mg/m^2 once-weekly (K56-1x) may potentially have fewer toxicities than K70-1x, particularly in conjunction with IMiDs. The recently published ARROW2 trial demonstrated comparable PFS with K56-1x versus K27-2x in the setting of Kd plus lenalidomide (KRd), with a PFS restricted mean survival time difference of only 3.3 days between the regimens in a randomized trial. However, the overall response rate with K56-1x versus K27-2x (82.5% versus 86.3%) did not meet the investigators' pre-specified non-inferiority threshold [16]. Furthermore, K56-1x has not been compared head-to-head against K70-1x.

Despite its widespread global use over the past decade, there is thus still no consensus on the most effective carfilzomib dosing schedule to achieve durable responses while minimizing toxicity and unnecessary clinic visits. While the ARROW trial did demonstrate the superiority of K70-1x over K27-2x, how K70-1x would compare against other modern dosing schedules – for example, K56-2x or K56-1x – is unknown. We thus performed a large retrospective observational study of real-world prescribing patterns and clinical outcomes for patients with RRMM to better identify the predictors and clinical impacts of different carfilzomib prescribing patterns.

METHODS

Patient selection and characterization

This study utilized the Flatiron Health electronic health record (EHR)-derived, real world longitudinal database, comprising de-identified patient-level structured and unstructured data, curated via technology-enabled abstraction. During the study period, the de-identified data originated from 280 academic and community cancer clinics across the United States (US). We included patients ages 18 to 70 years diagnosed between July 2012 (at the time of US Food and Drug Administration approval for carfilzomib) and June 2023 who were treated with a K-containing regimen in the second or subsequent line of therapy (LOT). Patients who received frontline carfilzomib, including as a component of first-line maintenance, were excluded.

Demographic characteristics included age at diagnosis, gender, race/ethnicity, practice type, Eastern Cooperative Oncology Group (ECOG) performance status (PS), International Staging System (ISS) stage, insurance type, presence versus absence of high-risk cytogenetic abnormalities (HRCAs), year of treatment initiation, renal function based on serum creatinine in milligrams per deciliter (mg/dL), and number of prior lines of therapy at carfilzomib initiation.

Cytogenetic status at treatment initiation was adapted from International Myeloma Working Group (IMWG) criteria [17], with HRCAs defined as del(17p), t(14;16), t(14;20), t(4;14), and gain(1q)/amp(1q). Renal function was categorized as normal (serum creatinine <1.3 mg/dL), renal insufficiency (serum creatinine between 1.3 and 2.9 mg/dL), or renal failure (serum creatinine ≥ 3.0 mg/dL).

Prescribing patterns

Carfilzomib dosage was defined based on the initial dose used at the beginning of the second week of the first cycle, given that the initial week's dose(s) are typically given at a starting dose of 20 mg/m^2. When carfilzomib dosing in mg/m^2 was not directly capturable from the EHR, total doses were converted to mg/m^2 dosing using the Mosteller body surface area (BSA) formula with height/weight data obtained within 30 days of the treatment episode. Once-weekly versus twice-weekly carfilzomib dosing was defined based on the presence or absence of consecutive-day dosing during each treatment week. Partner drugs that were prescribed within the same K-containing LOT were grouped into CD38 mAbs such as daratumumab or isatuximab, IMiDs such as lenalidomide or pomalidomide, other drugs such as cyclophosphamide and selinexor, and finally dexamethasone. Doublet regimens were defined as carfilzomib plus dexamethasone (Kd). Triplets were defined as Kd plus one other drug, and quadruplets were defined as Kd plus two other drugs. If carfilzomib dose schedules changed over time (e.g., de-escalation due to toxicities), only the first dosing schedule was used.

Given the wide heterogeneity in carfilzomib dosing regimens across trials, we intentionally chose to focus on three modern carfilzomib regimens for ease of comparisons. Carfilzomib 70 mg/m^2 once weekly (K70-1x) was chosen based on the ARROW trial, where this regimen was shown to outperform K27-2x [15]. Carfilzomib 56 mg/m^2 twice weekly (K56-2x) was chosen based on its use in ENDEAVOR, CANDOR, and IKEMA [6, 9, 10]. Finally, carfilzomib 56 mg/m^2 once weekly (K56-1x) was chosen based on its use in several recently published MM trials including MASTER, IsKia, SELECT, and ARROW2 [11, 16, 18, 19]. As shown in Supplementary Fig. 1, we also performed an exploratory analysis of all K dosing regimens in Flatiron data between July 2012 and June 2023 (including K56-1X, K56-2X, K70-1x, and other dosing schedules) to explore their usage over time. The conclusions of our manuscript did not change with the consideration of these regimens.

Endpoints and statistical analyses

The primary outcomes were real-world progression-free survival (rwPFS) and real-world overall survival (rwOS). rwPFS was defined as the time from carfilzomib initiation to the first derived date of progressive disease (PD), death, or censoring at the last assessment date. rwOS was defined as the time from carfilzomib initiation until death or censoring at the last confirmed EHR activity. PD was inferred based on IMWG criteria [20] using Flatiron analyses of serum protein electrophoresis, urine protein electrophoresis, or serum kappa and lambda free light chain (FLC) results as done previously [21]. Adverse effects within the K-containing LOT were derived using ICD-9 and ICD-10 codes for hypertension, congestive heart failure, pulmonary hypertension, and acute kidney injury.

Descriptive statistics were used to describe demographic, clinical, disease-specific, and treatment characteristics. Continuous variables were reported as medians and interquartile ranges (IQRs). Categorical variables were reported as number (n) and percent (%) of eligible patients. Multinomial logistic regression was used to assess factors associated with prescribing patterns, with K56-1x chosen as the reference prescribing pattern. Adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were summarized for each covariate. For survival analysis, median months from K-containing line initiation (index date) to rwPFS and rwOS were estimated using the Kaplan-Meier method. Cox proportional hazards models included transplant as a time-varying covariate and adjustment for other clinical and demographic factors. Adjusted hazard ratios (HR) and corresponding 95% confidence intervals (CI) were calculated. All analyses were performed with R Studio 2022, version 4.2.2.

RESULTS

Patient selection and characteristics

A flow diagram of included patients is shown in Fig. 1. There were a total of 17,694 patients with RRMM included in the Flatiron Health database, of whom 2420 (13.7%) received any type of K-containing regimen in any LOT. Of these patients, 486 (20.1%) received K56-1x, K56-2x, or K70-1x. As noted in Supplementary Fig. 1, these were indeed the three most common regimens in the year 2023 and were retained as the focus of our analysis. Our final data set comprised 136 (28.0%) patients who received K56-1x, 86 (17.7%) K56-2x, and 264 (54.3%) K70-1x. The breakdown of carfilzomib usage was roughly similar between second-line therapy ($n = 202$, 41.6%) and later lines ($n = 284$, 58.4%). There were no significant differences in the type of carfilzomib dosing based on LOT (Supplementary Fig. 2).

The baseline characteristics for the 486 analyzed patients are shown in Table 1. The median age at carfilzomib initiation was similar between cohorts: 67 years old (IQR 59-74) for K56-1x, 68 years old (IQR 60-76) for K56-2x, and 70 years old (IQR 62-76) for K 70-1x. The distribution of K-containing LOT was also similar between cohorts, with 55–60% of patients in each cohort receiving carfilzomib as their third LoT or later. Distributions of ECOG PS, renal impairment, International Staging System (ISS) staging, and presence of HRCAs were also similar between cohorts. As expected for our data source, most patients ($n = 358$, 73.7%) were treated at community centers. However, the distribution of dosing patterns differed by practice setting: patients receiving K56-1x were more commonly treated at academic centers (40.4%) compared to K56-2x (5.8%) and K 70-1x (12.5%).

In the multinomial logistic regression analysis, we found that the year of K-containing treatment initiation and practice type were statistically associated with lower odds of prescribing K56-2x

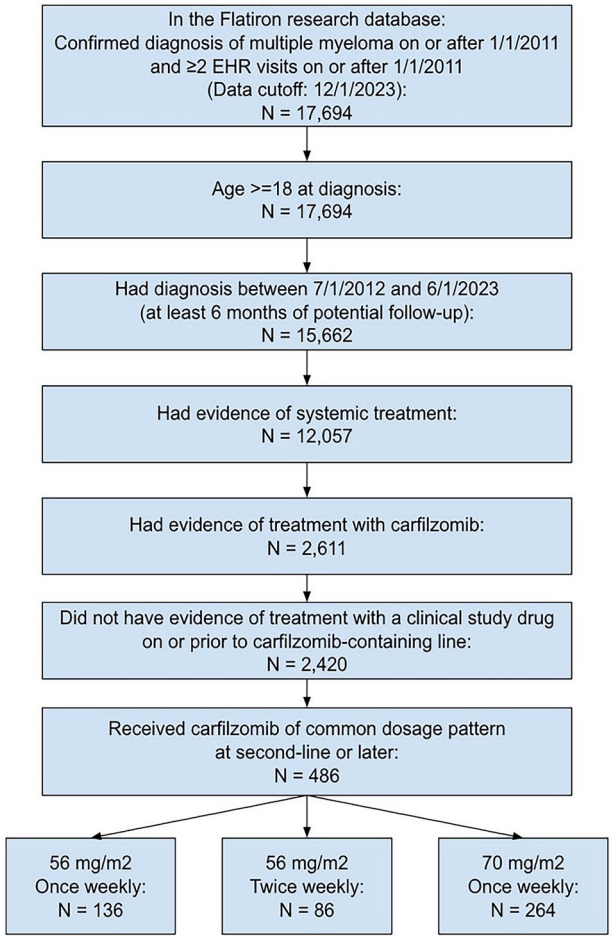

Fig. 1 Flow chart of analyzed patients.

or K70-1x versus K56-1x (Table 2). Higher ECOG PS was associated with lower odds of using K56-2x compared to K56-1x; the odds ratios for K56-2x versus K56-1x were 0.70 (95% CI 0.47-1.05) for ECOG PS 1 and 0.30 (95% CI 0.25-0.36) for ECOG PS ≥ 2 as compared to patients with ECOG PS 0. Patients insured by Medicare or Medicaid were more likely to receive K56-2x compared to patients with commercial insurance (OR: 1.89; 95% CI 1.45-2.48 and OR: 2.42; 95% CI 1.84-3.19 respectively). In terms of treatment regimens, carfilzomib monotherapy or doublet therapy with dexamethasone were statistically associated with higher odds of receiving K56-2x (OR: 1.89; 95% CI 1.43-2.51) and lower odds of K70-1x (OR: 0.63; 95% CI 0.45-0.88) compared to K56-1x. K-containing quadruplet regimens were associated with lower odds of receiving K56-2x (OR: 0.28; 95% CI 0.24-0.32) and K70-1x (OR: 0.28; 95% CI 0.16-0.47) than K56-1x.

Carfilzomib partner drugs and prescribing trends

As shown in Table 3, partner drugs used with carfilzomib varied between dosing cohorts. Overall, most patients (57.0%, $n = 277$) received carfilzomib as part of a triplet regimen. For example, CD38 mAbs with Kd were used in 30.7% of patients ($n = 149$) while IMiDs with Kd were used in 18.1% of patients ($n = 88$). However, K56-2x recipients were more likely to receive carfilzomib in the form of Kd doublet therapy (46.5%, $n = 40$) with only 4.7% ($n = 4$) receiving a quadruplet regimen for RRMM. In contrast, of 136 recipients of K56-1x dosing, only 15.4% ($n = 21$) received Kd doublet therapy while 19.1% ($n = 26$) received a quadruplet regimen. K70-1x ($n = 264$) recipients fell in between: 20.1% ($n = 53$) received Kd doublet therapy, 7.2% ($n = 19$) a quadruplet regimen, and the remaining 65.1% ($n = 172$) a triplet regimen.

Relative trends in K56-1x, K56-2x, and K70-1x administration for RRMM over the past decade are shown in Fig. 2. As shown, none of these regimens were received by analyzed patients until 2016. K56-2x was initially the most commonly used of the three, comprising 63.2% of all analyzed patients in 2016 and 80.0% in 2017: however, only 19 and 15 patients received one of these three K dosing regimens in each respective year. K56-1x and K70-1x both began to gain adoption from 2018 onwards. In 2023, for example, 50.6% of analyzed patients received K70-1x while 37.0% received K56-1x. In contrast, only 12.3% of analyzed patients received K56-2x in 2023. The relative prevalences of K56-1x, K56-2x, and K70-1x versus other carfilzomib dosing schedules are shown in Supplementary Fig. 1.

Measures of efficacy and toxicity

Kaplan-Meier curves of rwPFS and rwOS for each dosing regimen are shown in Fig. 3A, B, respectively. Median rwPFS was 12.98 months (95% CI 11.17–20.70 months) for K56-1x, 13.17 months (95% CI 8.97–28.09 months) for K56-2x, and 10.94 months (95% CI 9.92–15.28 months) for K70-1x. Differences in rwPFS were not statistically significant ($p = 0.46$). Median rwOS was 44.55 months [95% CI 30.23 months to not reached (NR)] for K56-1x, 49.05 months (95% CI 38.14–NR months) for K56-2x, and 39.16 months (95% CI 29.60–50.99 months) for K70-1x. Differences in rwOS were also not statistically significant ($p = 0.62$).

There were no statistically significant differences in either survival endpoint with K56-2x or with K70-1x versus the reference of K56-1x, after adjusting for other covariates (Table 4).

Selected carfilzomib-related toxicities were analyzed as shown in Table 5. The prevalence of hypertension ranged from 5.8-13.2% across prescribing patterns, with an average prevalence of 9.9% ($n = 48$). The prevalence of congestive heart failure ranged from 0.0-4.4% with 12 cases (2.5% of all patients) split between the K56-1x ($n = 6$, 4.4%) and K70-1x ($n = 6$, 2.3%) groups. For acute kidney injury, the prevalence was 4.1% ($n = 20$) overall and was primarily noted in patients receiving K70-1x and K56-1x. Pulmonary hypertension was only detected in 1.0% ($n = 5$) of the cohort, predominantly in the K56-1X group ($n = 3$, 2.2%). Differences in the prevalences of these adverse events were not statistically significant.

DISCUSSION

In our study of 486 patients with RRMM who received carfilzomib in the modern era, there were no differences in rwPFS or rwOS between once-weekly or twice-weekly carfilzomib dosing. K56-1x and K70-1x had similar efficacy profiles despite a higher dose intensity with the latter dosing schedule. Our study builds on the results of the ARROW and ARROW2 trials, which demonstrated the superiority of K70-1x over K27-2x and comparable PFS with K56-1x versus K27-2x [15, 16]. To our knowledge, only a single study has previously investigated the question of optimal carfilzomib dose in real-world practice. In this study of patients who received Kd doublet therapy between 2013 and 2017, both K56-2x and K70-1x were associated with longer time to treatment over the "legacy" K27-2x schedule [22]. However, K-containing triplets or quadruplets were not included in that study, and only 9% of analyzed patients had received a modern carfilzomib dosing schedule. Interestingly, while the previous study did not report the breakdown of K56-2x versus K70-1x when paired with dexamethasone, we found that K56-2x was more likely than K70-1x among patients in our cohort who received a doublet.

One striking finding in our analysis is the rising prominence of K56-1x in RRMM even within the context of modern carfilzomib dosing schedules (K56-1x, K56-2X, or K70-1x). In comparing the adoption of these modern carfilzomib dosing schedules, for example, the use of K56-2x has fallen from 80% in 2017 to 12% in 2023 while K56-1x has risen from 7% to 37% in this period. This

Table 1. Baseline patient characteristics by carfilzomib prescribing pattern.

Baseline characteristics	Total ($n = 486$)	K56-1x ($n = 136$)	K56-2x ($n = 86$)	K70-1x ($n = 264$)	p value
Age (median, IQR)					
At diagnosis	66 (58–72)	65 (57–71)	66 (58–72)	67 (59–73)	0.224
At index, K initiation	68 (61–75)	67 (59–74)	68 (60–76)	70 (62–76)	0.135
Line of treatment (*n*, %)					0.788
Second-line	202 (41.6%)	59 (43.4%)	37 (43.0%)	106 (40.2%)	
Third-line or beyond	284 (58.4%)	77 (56.6%)	49 (57.0%)	158 (59.8%)	
Gender (*n*, %)					0.186
Male	268 (55.1%)	66 (48.5%)	49 (57.0%)	153 (58.0%)	
Female	218 (44.9%)	70 (51.5%)	37 (43.0%)	111 (42.0%)	
Ethnicity (*n*, %)					0.091
White, non-Latinx	267 (54.9%)	82 (60.3%)	39 (45.3%)	146 (55.3%)	
Non-White	219 (45.1%)	54 (39.7%)	47 (54.7%)	118 (44.7%)	
Practice type (*n*, %)					<0.001*
Community	358 (73.7%)	68 (50.0%)	77 (89.5%)	213 (80.7%)	
Academic	93 (19.1%)	55 (40.4%)	($n \leq 5$)	33 (12.5%)	
Both	35 (7.2%)	13 (9.6%)	($n \leq 5$)	18 (6.8%)	
Insurance status (*n*, %)					0.163
Commercial	70 (14.4%)	18 (13.2%)	9 (10.5%)	43 (16.3%)	
Medicare	269 (55.3%)	71 (52.2%)	46 (53.5%)	152 (57.6%)	
Medicaid	30 (6.2%)	6 (4.4%)	10 (11.6%)	14 (5.3%)	
Other Payer	45 (9.3%)	17 (12.5%)	6 (7.0%)	22 (8.3%)	
Unknown/uninsured	72 (14.8%)	24 (17.6%)	15 (17.4%)	33 (12.5%)	
ECOG PS (*n*, %)					0.125
0	151 (31.1%)	36 (26.5%)	30 (34.9%)	85 (32.2%)	
1	204 (42.0%)	62 (45.6%)	37 (43.0%)	105 (39.8%)	
≥2	71 (14.6%)	20 (14.7%)	($n \leq 5$)	46 (17.4%)	
Unknown	60 (12.3%)	18 (13.2%)	14 (16.3%)	28 (10.6%)	
Serum creatinine					0.082
≤1.2 mg/dL	246 (50.6%)	80 (58.8%)	40 (46.5%)	126 (47.7%)	
1.3–2.9 mg/dL	81 (16.7%)	19 (14.0%)	14 (16.3%)	48 (18.2%)	
≥3.0 mg/dL	21 (4.3%)	($n \leq 5$)	($n \leq 5$)	17 (6.4%)	
Unknown	138 (28.4%)	34 (25.0%)	31 (36.0%)	73 (27.7%)	
Paraprotein (*n*, %)					0.488
IgG	278 (57.2%)	81 (59.6%)	49 (57.0%)	148 (56.1%)	
IgA	113 (23.3%)	30 (22.1%)	16 (18.6%)	67 (25.4%)	
Light chain only	81 (16.7%)	19 (14.0%)	18 (20.9%)	44 (16.7%)	
Other/unknown	14 (2.9%)	6 (4.4%)	($n \leq 5$)	($n \leq 5$)	
ISS stage (*n*, %)					0.295
Stage I	121 (24.9%)	35 (25.7%)	20 (23.3%)	66 (25.0%)	
Stage II	102 (21.0%)	36 (26.5%)	15 (17.4%)	51 (19.3%)	
Stage III	118 (24.3%)	29 (21.3%)	18 (20.9%)	71 (26.9%)	
Unknown	145 (29.8%)	36 (26.5%)	33 (38.4%)	76 (28.8%)	
HRCA					0.294
Absent	289 (59.5%)	84 (61.8%)	56 (65.1%)	149 (56.4%)	
Present	197 (40.5%)	52 (38.2%)	30 (34.9%)	115 (43.6%)	
Prior transplant (*n*, %)					0.406
Yes	130 (26.7%)	42 (30.9%)	20 (23.3%)	68 (25.8%)	
No	356 (73.2%)	94 (69.1%)	66 (76.7%)	196 (74.2%)	

Statistical testing was done at a significance level of $p = 0.05$. ANOVA test was used for continuous variables, and Chi-square test and Fisher's exact test were used for categorical variables. Percentages are calculated based on total in each dosing group (column totals). Subgroups with $n \leq 5$ patients are masked to protect patient privacy.

*Significant at $p < 0.05$.

ECOG PS Eastern Cooperative Oncology Group performance status, *HRCA* high risk cytogenetic abnormalities defined as deletion 17p, t(14;16), t(14;20), t(4;14), gain(1q)/amp(1q), *IQR* interquartile range, *ISS* International Staging System, *K56-2x* carfilzomib 56 milligrams per meter squared twice weekly, *K70-1x* carfilzomib 70 milligrams per meter squared once weekly, *mg/dL* milligrams per deciliter.

Table 2. Multivariable analyses of carfilzomib prescribing patterns.

Characteristic	K56-2x (vs K56-1x)		K70-1x (vs K56-1x)	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Age at diagnosis	0.98 (0.95–1.01)	0.162	1.01 (0.98–1.03)	0.631
Gender				
Male	1.00	–	1.00	–
Female	0.94 (0.61–1.46)	0.784	0.73 (0.50–1.07)	0.102
Race/Ethnicity				
White, non-Latinx	1.00	–	1.00	–
Non-White	1.56 (1.08–2.24)	0.017*	1.13 (0.79–1.61)	0.516
Practice type				
Community	1.00	–	1.00	–
Academic	0.06 (0.05–0.07)	<0.001*	0.15 (0.10–0.24)	<0.001*
Both	0.35 (0.32–0.40)	<0.001*	0.48 (0.33–0.69)	<0.001*
Insurance type				
Commercial	1.00	–	1.00	–
Medicare	1.89 (1.45–2.48)	<0.001*	0.79 (0.57–1.10)	0.162
Medicaid	2.42 (1.84–3.19)	<0.001*	0.74 (0.52–1.05)	0.094
Other payer	0.67 (0.55–0.80)	<0.001*	0.46 (0.31–0.68)	<0.001*
Unknown/None	1.52 (1.16–1.99)	0.002	0.71 (0.48–1.04)	0.080
ECOG performance status				
0	1.00	–	1.00	–
1	0.70 (0.47–1.05)	0.081	0.75 (0.53–1.06)	0.105
≥2	0.30 (0.25–0.36)	<0.001*	1.16 (0.74–1.80)	0.523
Unknown	2.64 (2.00–3.48)	<0.001*	1.35 (0.91–2.00)	0.141
ISS stage				
Stage I	1.00	–	1.00	–
Stage II	0.40 (0.29–0.56)	<0.001*	0.60 (0.41–0.87)	0.007*
Stage III	0.66 (0.49–0.88)	0.004*	0.92 (0.66–1.30)	0.650
Unknown	0.75 (0.49–1.16)	0.199	0.71 (0.49–1.01)	0.059
HRCA status				
None	1.00	–	1.00	–
Present	0.79 (0.53–1.19)	0.265	1.07 (0.74–1.56)	0.724
Serum creatinine				
≤1.2 mg/dL	1.00	–	1.00	–
1.3–2.9 mg/dL	1.10 (0.81–1.48)	0.552	1.43 (0.93–2.21)	0.106
≥3 mg/dL	0.66 (0.64–0.67)	<0.001*	2.89 (2.72–3.07)	<0.001*
Unknown	1.49 (0.98–2.27)	0.061	1.00 (0.67–1.52)	0.982
Index year (K initiation)	0.65 (0.65–0.65)	<0.001*	0.91 (0.91–0.91)	<0.001*
Line of treatment				
2 L	1.00	–	1.00	–
3 L+	1.20 (0.78–1.86)	0.405	1.24 (0.85–1.82)	0.269
Concurrent therapy				
Triplet	1.00	–	1.00	–
Single/doublet	1.89 (1.43–2.51)	<0.001*	0.63 (0.45–0.88)	0.006*
Quadruplet	0.28 (0.24–0.32)	<0.001*	0.28 (0.16–0.47)	<0.001*
Other	0.63 (0.54–0.75)	<0.001*	0.38 (0.24–0.59)	<0.001*

Adjusted for age at diagnosis, gender, race/ethnicity, practice type, insurance type, ECOG PS at 1 L, ISS stage, presence or absence of HRCAs, year of index line, index line number, partner drug type, transplant after index, and serum creatinine level; Treatment reference group: 56 mg/m^2 once weekly (K56-1X) at 2 L+.
*Significant at $p < 0.05$.
CI confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *HRCA* high risk cytogenetic abnormalities defined as deletion 17p, t(14;16), t(14;20), t(4;14), gain(1q)/amp(1q), *ISS* International Staging System, *K56-2x* carfilzomib 56 milligrams per meter squared twice weekly, *K70-1x* carfilzomib 70 milligrams per meter squared once weekly, *mg/dL* milligrams per deciliter, *OR* odds ratio.

Table 3. Carfilzomib partner drugs in RRMM dosing schedules.

Partner drug	Total ($n = 486$)	K56-1x ($n = 136$)	K56-2x ($n = 86$)	K70-1x ($n = 264$)
Overall K-containing regimen				
Quadruplet	49 (10.1%)	26 (19.1%)	4 (4.7%)	19 (7.2%)
Triplet	277 (57.0%)	68 (50.0%)	37 (43.0%)	172 (65.1%)
Doublet	114 (23.5%)	21 (15.4%)	40 (46.5%)	53 (20.1%)
Other or unspecified	46 (9.5%)	21 (15.4%)	5 (5.8%)	20 (7.6%)
K-containing quadruplets				
CD38 mAb, K, IMiD, dex	49 (10.1%)	26 (19.1%)	4 (4.7%)	19 (7.2%)
K-containing triplets				
CD38 mAb, K, dex	149 (30.7%)	19 (14.0%)	26 (30.2%)	104 (39.4%)
K, IMiD, dex	88 (18.1%)	36 (26.5%)	10 (11.6%)	42 (16.0%)
Other K triplet	40 (8.2%)	13 (9.6%)	1 (1.2%)	26 (9.9%)
K-containing doublet				
Kd	108 (22.2%)	18 (13.2%)	40 (46.5%)	50 (18.9%)
Kd, then K monotherapy	6 (1.2%)	3 (2.2%)	0 (0.0%)	3 (1.1%)
Other or unspecified	46 (9.5%)	21 (15.4%)	5 (5.8%)	20 (7.6%)

All regimens contain dexamethasone, as specified with "d", except for K + "Other PI", K + Anti-BCMA and K + Other mAb doublet therapy and K single agent therapy (K-single). Percentages are calculated based on total in each dosing group (column totals).
Dex dexamethasone, *IMiD* immunomodulatory imide drug, *K* carfilzomib, *K56-1x* carfilzomib 56 milligrams per meter squared once weekly, *K56-2x* carfilzomib 56 milligrams per meter squared twice weekly, *K70-1x* carfilzomib 70 milligrams per meter squared once weekly, *Kd* carfilzomib dexamethasone, *mAb* monoclonal antibody.

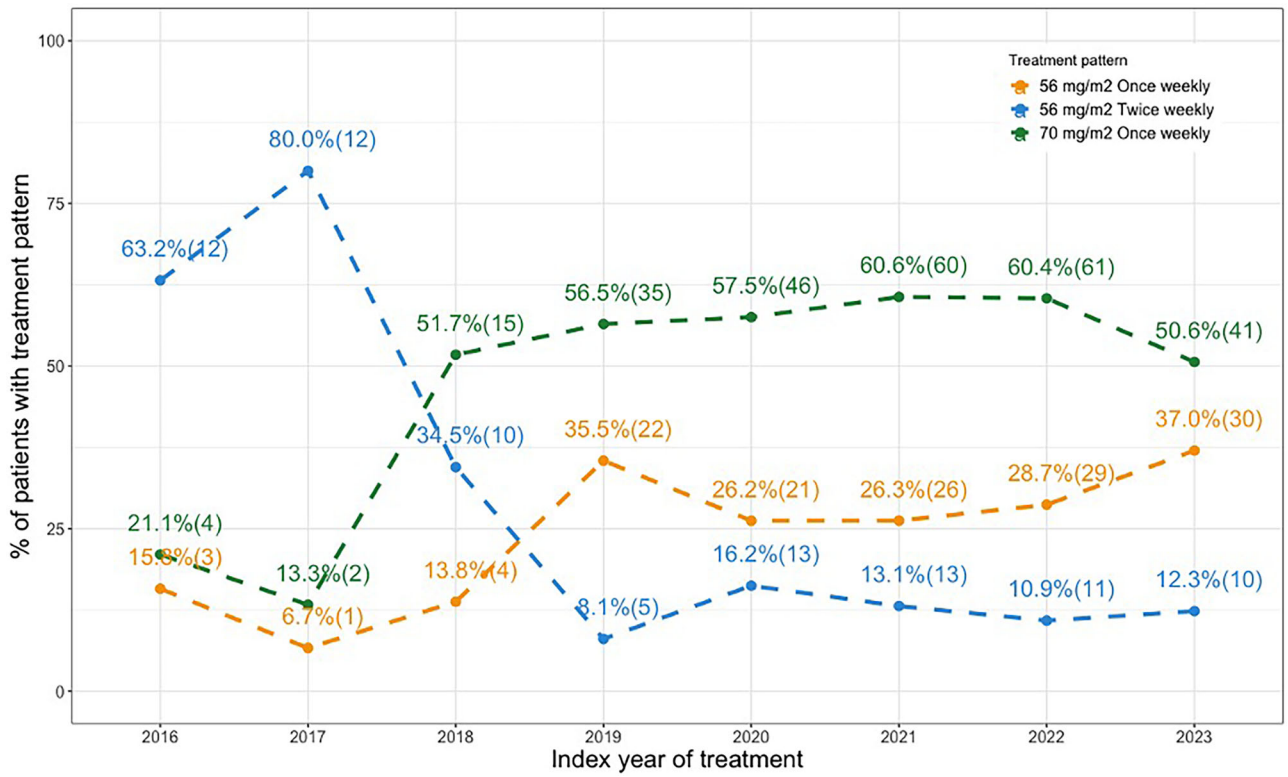

Fig. 2 Trends in carfilzomib usage over time in RRMM.

finding is true even though most recent Phase 3 trials of carfilzomib in RRMM (e.g., CANDOR and IKEMA) have used K56-2x [9, 10]. Unlike a similar real-world analysis of bortezomib in MM by our group [21], the relative proportions of once-weekly versus twice-weekly carfilzomib dosing increased gradually over the past decade rather than abruptly in 2020 with efforts to reduce clinic visits during the COVID-19 pandemic. This may be due to the significant 'time toxicity' of MM therapy particularly in the relapsed/refractory setting [23, 24] as a reason to support once-weekly dosing. With regard to why K56-1x may eventually surpass K70-1x as a dosing choice, K70-1x may be associated with low-grade adverse events (e.g., mild neutropenia or post-treatment nausea) that prompt providers to choose K56-1x for future patients. While this assertion is difficult to prove in the absence

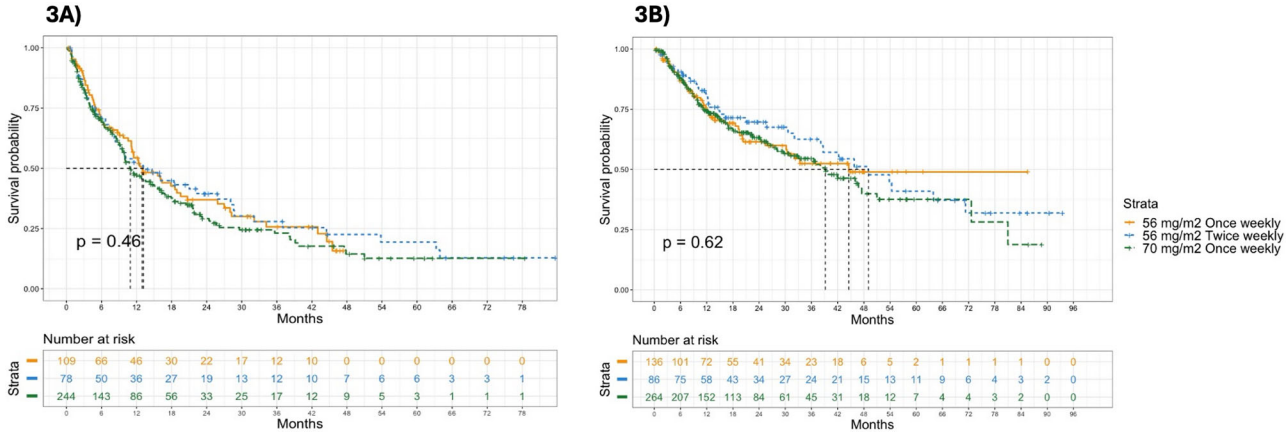

Fig. 3 Outcomes based on carfilzomib prescribing pattern. Kaplan–Meier curves of real-world progression-free survival (rwPFS) are shown in and real-world overall survival (rwOS) are shown in.

Table 4. Multivariate analysis of carfilzomib prescribing patterns and survival outcomes.

	# patients	Median (months) (95% CI)	HR (95% CI)	*p* value
rwPFS				
K56-1x	109	12.98 (11.17–20.70)	1.00 (ref)	–
K56-2x	78	13.17 (8.97–28.09)	0.95 (0.63–1.43)	0.810
K70-1x	244	10.94 (9.92–15.28)	0.97 (0.71–1.33)	0.861
rwOS				
K56-1x	136	44.55 (30.23–N/A)	1.00 (ref)	
K56-2x	86	49.05 (38.14–N/A)	0.61 (0.36–1.02)	0.058
K70-1x	264	39.16 (29.60–50.99)	0.73 (0.50–1.08)	0.113

Adjusted for age at diagnosis, gender, race/ethnicity, practice type, insurance type, ECOG PS at 1 L, ISS stage, presence or absence of HRCAs, year of index line, partner drug type, and serum creatinine level. Treatment reference group: 56 mg/m^2 once weekly (K56-1x) prescribing at index line.
CI confidence interval, *ECOG PS* Eastern Cooperative Oncology Group performance status, *HR* hazard ratio, *HRCA* high-risk cytogenetic abnormality, *K56-1x* carfilzomib 56 milligrams per meter squared once weekly, *K56-2x* carfilzomib 56 milligrams per meter squared twice weekly, *K70-1x* carfilzomib 70 milligrams per meter squared once weekly, *rwPFS* real-world progression free survival, *rwOS* real-world overall survival.

Table 5. Toxicity of each carfilzomib prescribing pattern.

Adverse effect (*n*, %)	Total (*n* = 486)	K56-1x (*n* = 136)	K56-2x (*n* = 86)	K70-1x (*n* = 264)	*p* value
Hypertension	48 (9.9%)	18 (13.2%)	5 (5.8%)	25 (9.5%)	0.186
Congestive heart failure	12 (2.5%)	6 (4.4%)	0 (0.0%)	6 (2.3%)	0.116
Pulmonary hypertension	5 (1.0%)	3 (2.2%)	0 (0.0%)	2 (0.8%)	0.314
Acute kidney injury	20 (4.1%)	9 (6.6%)	1 (1.2%)	10 (3.8%)	0.136

K56-1x carfilzomib 56 milligrams per meter squared once weekly, *K56-2x* carfilzomib 56 milligrams per meter squared twice weekly, *K70-1x* carfilzomib 70 milligrams per meter squared once weekly.

of a randomized trial, a non-randomized comparison of K56-1x and K70-1x (in a Phase 1b dose-escalation study of KRd regimens) showed that carfilzomib dosing was lowered in 48% of patients receiving K70-1x versus only 20% of patients receiving K56-1x [25].

Our study is the largest and most extensive real-world analysis of modern carfilzomib dosing schedules to date. However, given its retrospective design and EHR data source, there are several limitations. Although we were able to capture ECOG PS, we did not capture other variables such as frailty or patient apprehension about cardiac adverse events (AEs) that may have influenced the selection of dosing. Similarly, physicians may have chosen K 70-1x preferentially for patients with high disease burden who would have also been likely to have shorter durations of responses. With regard to toxicity assessments, our assessment of carfilzomib-related AEs is limited by our reliance on structured ICD codes and our inability to differentiate adverse events versus pre-existing conditions (for example, treatment-emergent cardiomyopathy versus pre-existing heart failure). Because we focused on the three most common RRMM regimens in the modern era, our conclusions may not apply to less commonly used regimens such as twice-weekly 36 mg/m^2. Our findings are similarly not necessarily applicable to the frontline or maintenance settings. In the maintenance setting (including in RRMM after sufficient time to achieve best response), for example, once-weekly or every-two-week carfilzomib dosing is undoubtedly the norm [11, 26, 27].

In conclusion, our large study shows that once-weekly carfilzomib dosing has become the most common standard of care for RRMM treatment in the US. Our findings suggest that higher doses or more frequent dosing of carfilzomib beyond K56-1x are not associated with better clinical outcomes in the real-world setting. Carfilzomib 56 mg/m^2 dosed once weekly may provide the best balance of efficacy, safety, and reduced "time toxicity" from infusion visits. Similarly, adopting K56-1x in trials and guidelines may reduce disparities in the treatment of

relapsed/refractory MM [28]. In the absence of further data from randomized trials, our findings support the continued use of carfilzomib 56 mg/m^2 in MM both in clinical trials and routine practice.

DATA AVAILABILITY

The data that support the findings of this study have been originated by Flatiron Health, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to dataaccess@flatiron.com.

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AUTHOR CONTRIBUTIONS

SD, RB, MW, XW and GK were responsible for study design. MW and XW performed the statistical analyses. SD, RB, AMK, MW, XW, AA, and GK interpreted the study results. SD, RB and MW wrote the manuscript. RB, GK and XW supervised the study. All authors (SD, RB, AMK, MW, XW, AA, AA, MJ, BW, AJC, ASS, LDA, SVR, GK) reviewed the manuscript and provided valuable feedback. All authors (SD, RB, AMK, MW, XW, AA, AA, MJ, BW, AJC, ASS, LDA, SVR, GK) approved the final version.

COMPETING INTERESTS

RB: Consulting: Adaptive, BMS, Caribou Biosciences, Genentech, Gilead/Kite, GSK, Janssen, Karyopharm, Legend Biotech, Pfizer, Poseida Therapeutics, Sanofi, SparkCures; Research: Abbvie, BMS, Janssen, Novartis, Pack Health, Prothena, Sanofi. AMK: Research: Sanofi, Janssen. XW: Employment: Flatiron Health, Inc. (independent subsidiary of the Roche Group), stock ownership, Roche. MW: Employment: Flatiron Health, Inc. (independent subsidiary of the Roche Group), stock ownership, Roche. AA: Employment: Flatiron Health, Inc. (independent subsidiary of the Roche Group), stock ownership, Roche. MJ: Consulting: Janssen, BMS, Legend. Research: Janssen, BMS, Fate Therapeutics. ASS: Consulting: Novartis. LDA Jr: Consulting: Janssen, Celgene, BMS, Amgen, GSK, AbbVie, Beigene, Cellectar, Sanofi, Prothena. Research: BMS, Celgene, GSK, Janssen, Abbvie. AJC: Consulting: BMS, Adaptive; Research: Adaptive Biotechnologies, Harpoon, Nektar, BMS, Janssen, Sanofi, AbbVie. GK: Consulting: BMS, Arcellx, Sanofi, Janssen, Cellectar, Pfizer, Kedrion; Research: BMS, Janssen, Abbvie. GK: Consulting: BMS, Arcellx, Sanofi, Janssen, Cellectar, Pfizer, Kedrion, Kite; Research: BMS, Janssen, Abbvie, Arcellx. The remaining authors have no disclosures to report.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

All methods were performed in accordance with the relevant guidelines and regulations. This retrospective study was reviewed and exempted by the University of Texas Southwestern Institutional Review Board without the need for individual

patient consent. No patient-identifiable information was shared during analyses or are present in this manuscript.

ADDITIONAL INFORMATION

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