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RESEARCH

Continous or fixedcarfilzomib, lenalidomide and dexamethasone (krd) for relapsed-refractory multiple myeloma: long-term follow-up from a multicenter, retrospective real-life surveyfrom European myeloma network (emn) Italy

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Abstract

Based on the results of the ASPIRE trial, the KRd regimen (carfilzomib, lenalidomide and dexamethasone) has been approved in Italy for relapsed/refractory multiple myeloma (RRMM) patients since 2016. The published KRd schedule indicates this combination for 18 cycles, followed by continuous Rd until progression. However, in Italy, there are no limits to the number of KRd cycles, fully refunded based on negotiation with the Italian regulatory agency, and in some centers this combination has been used continuously, beyond the 18th cycle (continuous KRd, cKRd). To evaluate and compare safety and efficacy of both continuous and fixed KRd, we retrospectively collected real-world data from 356 patients treated in 20 EMN (European Myeloma Network) Italian centers from October 2016 to September 2023 and we patients treated with cKRd with those treated with the ASPIRE schedule. After a median follow-up of 48.59 months (CI 27.24–61.24), the overall response rate (ORR) of the entire series was 83% with 35% of complete responses(CR). The mPFS was 23.1 months (CI 20.11–28.62) and mOS was 62.85 months (CI 53.75–70.34), longer than the mOS of the ASPIRE study (48.3 months). The landmark analysis of the cKRd population shows non-significant benefit both in terms of PFS and OS compared to patients where the administration of KRd was stopped at the 18th cycle as in the ASPIRE trial, to note, in the cKRd group patients had a more aggressive disease based on ISS and R-ISS stage. Therefore, although we did not observe additional toxicities, our retrospective analysis, while confirming the validity of the KRd regimen in RRMM, does not indicate any general advantage in keeping the administration of carfilzomib beyond the ASPIRE schedule.

Keywords Relapse/Refractory multiple myeloma · Carfilzomib-Lenalidomide-Dexamethasone (KRd) · Continuous KRd (cKRd) · Real world evidence

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Introduction

Proteasome inhibitors and immunomodulators together with monoclonal antibodies have significantly improved outcome of RRMM patients but, despite effective triplet and quadruplet combinations, most patients end up relapsing [1–3].Carfilzomib is a selective proteasome inhibitor (PI) whose efficacy emerged in the past from the randomized phase III ENDEAVOR and ASPIRE trials in combination with dexamethasone and with lenalidomide and dexamethasone, respectively [4–6]. Based on the results of these two trials, carfilzomib has become one of the backbones of RRMM treatment.

In the ASPIRE trial, patients with RRMM after 1–3 prior LOT were randomized to receive KRd or Rd in 28-day cycles keeping on with only Rd after 18 cycles. Median OS was 48.3 months for KRd versus 40.4 months for Rd; median PFS was 26.1 months versus 16.6 months [5]– [6]. Thanks to these results, actually KRd triplet is investigated in some clinical trials alone or in combination with other agents such as anti-CD38 antibodies to improve its efficacy in high-risk MM patients [7]. In addition, several trials are investigating its use in combination in upfront lines of therapy [8]– [9]. Based on the results of the ASPIRE trial, KRd was approved in 2015 by the European Medicines Agency and in 2016 by Italian drug agency for RRMM patients but no limit to the number of KRd cycles was sat up, and in some centers this combination has been used continuously, beyond the 18th cycle (cKRd)and this was aided by the fact that after the 18th cycle carfilzomib was provided free of charge by the manufacturer.

Since in first-line setting, such as the randomised phase 2 FORTE trial [10] and in RRMM (5) setting continuous therapy allows better disease control over time [11–16]we have designed a national survey to investigate safety and feasibility of cKRd and fixed KRd, based on a retrospective collection of real-world data from 356 patients treated in 20 EMN Italian centers.

Materials and methods

Study design and participants

This real-world, retrospective, observational survey was conducted on 356 patients at 20 Italian centers belonging to European myeloma network, Italy, from October 2016 to September 2023. Adults (≥18 years of age) with RRMM who had been prescribed carfilzomib, lenalidomide and dexamethasone in routine clinical practice were eligible for inclusion. Patients had received at least one prior LOT. Patients were evaluated as relapsed or refractory to the previous treatment based on the International Myeloma Working Group (IMWG) guidelines criteria [17].The study was conducted in accordance with the principles of the Declaration of Helsinki. Informed consent for data processing was obtained from all patients.

An antibiotic and antiviral prophylaxis was carried out with trimethoprim and sulfamethoxazole (800 mg twice a day, twice a week) and acyclovir 200, 400 or 800 mg daily according to the policy of each center. Supportive therapy with erythropoietin (EPO) and granulocyte colony-stimulating factor (G-CSF) was administered accordingly to ASH/ASCO guidelines and policy of each single center. All patients were vaccinated against COVID19 infection, based on the availability of vaccines in each center [18–20]. All patients underwent a baseline cardiovascular evaluation with visit and echocardiogram and subsequently as clinically indicated [21].

Data were collected from the first administration of carfilzomib until patients' death, withdrawal of consent or loss to follow-up.Study data were collected and managed using REDCap electronic data capture [22].

Each center independently decided wheter to stop treatment at cycle 18 or continue based on their personal experience in treating MM patients at relapse. Decisions were made at the initiation or during treatment as for physician's choice, indipendently by the response at cycle 18.

We evaluated safety and feasibility of KRd given up to 18 cycles, compared to a small group of patients treated continuously until progression or intolerance, outside of clinical trials.

Statistical analysis

Patient's characteristics were summarized by frequencies and percentage values for categorical variables, while continuous variables were described with median values and their relative ranges (minimum, maximum). Univariate comparisons were performed according to the Pearson's Chi-squared test or Fisher's exact test for categorical variables and Wilcoxon rank sum test for continuous variables. Overall survival (OS) was defined as the time from the first administration of therapy to death from any cause or the date of the last follow-up. Progression-free survival (PFS) was defined as the time elapsed between treatment initiation and disease progression or death from any cause, with censoring of patients who are lost to follow-up. The probabilities of OS and PFS were estimated following the Kaplan–Meier product limit method, while the results of univariate comparisons were performed according to the Log-Rank test. All tests were two-sided with a significance level of 0.05, and confidence intervals were calculated at a 95% level. All analyses were performed using the R version 4.2.2.

Results

Patients' characteristics

In this retrospective, multicenter study, we evaluated safety and efficacy of 356 RRMM patients treated with the association of carfilzomib, lenalidomide and dexamethasone after at least one prior LOT.Based on physician's choice, of the 137 patients who reached the 18th cycle, 101 (74%) received cKRd, including 79 (58%) treated for 24 and 17 (12%) for 36 or more cycles. All patients who extended treatment beyond 18 cycles signed a specific informed consent.Data on cytogenetic abnormalities at diagnosis, detected by fluorescence in-situ hybridization on highly purified bone marrow plasma cells, evaluating the t(4;14), t(14;16), t(11;14) and del(17p) only, allowed the subdivision of patients into the R-ISS staging system and was performed on 145 patients. Most frequent comorbidities included arterial hypertension (14%) and diabetes (5%). The median age was 63 (range 34–87) with 53% of males (190 patients) and 47% of females (166 patients). 156 patients (44%) were ≥65 years old and 75(21%) were ≥70 years. The median number of prior LOT was 3 (range 1–11), including 230 (69%) patients who undergone autologous stem-cell transplant (ASCT). Of these, 154 (46%) received fewer than 3 prior LOT, while 64 (19%) received 5 lines or more. According to the ISS stage, the 300 evaluable patients appeared equally divided (32%, 33% and 35% for stage I, II and III respectively). Furthermore, of 145 patients evaluable for R-ISS, 25% were stage I, 48% stage II and 28% stage III. Only 4% of patients were undergoing dialysis and 14% had extramedullary disease.

Demographic and disease characteristics are shown in Table 1.All patients received intravenous carfilzomib at the dose of 20 mg/m2 (lasting 30 min) on days 1 and 2, then of 27 mg/m2 on days 8, 9, 15 16 of the first cycle; then it was administered on days 1, 2, 8, 9, 15 and 16 of the subsequent up to the 12th cycle, going on at the same dosage on days 1, 2, 15 and 16 since 13th cycle; dexamethasone 20 mg was administered orally on the same days of carfilzomib; lenalidomide 25 mg daily orally was given on days 1–21 of each 28-day cycle. Treatment was planned until progression (cKRd) or, according to the ASPIRE schedule (KRd), for 18 months followed by treatment with lenalidomide and dexamethasone until progression or intolerance. The choice to stop or prolong treatment until progression was made by each center based on personal experience.In cases of specific predefined hematological and non-hematological toxic events, carfilzomib, lenalidomide and dexamethasone dosages were reduced, according to the manufacturers' recommendations and medical choice.The median number of KRd administered cycles was 12 and the best response was in median at cycle 4 (Table 1). Patients who received 1 or 2 prior LOT had a median number of KRd cycles of 17 whereas patients with ≥3 prior LOT received a median of 10 cycles ($p=0.001$). Of the 337 patients evaluable for number of prior LOT, 202 (60%) received less than 18 cycles and 135 (40%) received ≥18 cycles, with 78 (23%) who reached the 24th cycle or more and 17 (5%) the 36th; 49 of the 78 patients with at least 24 cycles had received 1 or 2 prior LOT and 29 patients > 2 prior LOT.In Table 2 we describe the clinical characteristics of patients in the two groups (fixed and continuous KRd). Considering that our survey is not a randomized clinical trial, the two groups appear substantially balanced for most characteristics; the cKRd group appears to have a more aggressive disease at diagnosis based on the ISS and R-ISS staging system, although the difference is not statistically significant.

Safety

Most frequent hematological adverse events (AEs), evaluated based on CTCAE criteria [23],(27) included anemia (11.5%), neutropenia (20.4%), and thrombocytopenia (16.3%). Most frequent (> 10%) non-hematological AEs were infections (22.9%), gastrointestinal toxicities (14.8%), and pneumonia (11.9%), with a total of 157 patients (44%) experienced a grade 3–4 toxicity. Hypertension was seen in 26 (7.3%) patients with only 0.3% grade 3–4, while neuropathy was seen in 25 (7%) patients (Table 3). Gastrointestinal toxicities were mainly represented by diarrhea, probably associated with lenalidomide. Of note, we've seen only 0.3% and 3.1% Grade 3–4 AEs for hypertension and cardiovascular complications. We did not observe any significant worsening of grade 3–4 hematological or non-hematological AEs in cKRd patients. There was no significant difference in terms of incidence of grade 3–4 AEs in the populations with < 3 and ≥3 prior lines. The number of deaths was 12 in the general population, with 8 (6.9%) vs. 4 (2.2%) in the < 3 and ≥3 prior LOT.

Efficacy

The ORR (≥PR) in the entire population was 83% (274 patients) with CR 36% (112 patients). The rates of CR and ORR were comparable between cKRd vs. fixed time KRd, with a CR of 62% vs. 68% and ORR of 99% vs. 96% respectively (Table 2).

Taking in account the number of prior LOT, the rate of CR was higher in the group with < 3 (64 patients, 45%) respect to those with ≥3 (48 patients, 29%) ($p=0.002$), as well as the ORR (128 patients, 91% vs. 130 patients, 78%) ($p=0.002$). PD was seen in 42 patients (36%) of those with < 3 prior LOT vs. 107 patients (60%) of the ≥3 prior

Table 1 Patients' characteristics

Characteristic	*N* = 356
Sex, *n* (%)	
Male	190 (53%)
Female	166 (47%)
Age, median (range)	63 (34, 87)
Age (70), n (%)	
> 70ys	75 (21%)
≤70ys	281 (79%)
Age (65), n (%)	
> 65ys	156 (44%)
≤65ys	200 (56%)
Interval between diagnosis and KRd, median (range, years)	3.3 (0.2–24.2)
Unknown	12
ISS at diagnosis, n (%)	
I	96 (32%)
II	100 (33%)
III	104 (35%)
Unknown	56
r-ISS at diagnosis, n (%)	
I	36 (25%)
II	69 (48%)
III	40 (28%)
Unknown	211
Use of Zoledronic acid, n (%)	239 (73%)
Unknown	28
Previous Autologous, n (%)	230 (69%)
Previous Allogenic, n (%)	6 (2%)
Unknown	21
Number of Therapy lines, median (range)	3 (1, 11)
Unknown	19
Number of Previous Therapy lines (3), n (%)	
< 3 lines	154 (46%)
≥3 lines	183 (54%)
Unknown	19
Number of Previous Therapy lines (5), n (%)	
< 5 lines	273 (81%)
≥5 lines	64 (19%)
Unknown	19
Previous exposure to:	319 (89%)
PIs	66 (18.5%)
IMids	17 (5%)
-Lenalidomide	15 (4%)
-Pomalidomide	16 (4.5%)
MoAbs	17 (5%)
Polichemotherapy	
Bendamustine	
Histological Type, n (%)	
IgG	198 (70%)
IgM	4 (1.4%)
IgA	76 (27%)
IgE	2 (0.7%)
IgD	1 (0.4%)
Unknown	75
Light Chain involved, n (%)	
Lambda	123 (35%)
Kappa	226 (65%)
Unknown	7

Table 1 (continued)

Characteristic	*N*=356
Sex, *n* (%)	
Patients in Dialysis, n (%)	13 (4.0%)
Unknown	27
Extramedullary disease, n (%)	46 (14%)
Unknown	31

ISS Internationa Staging System, *R-ISS* Revised-Internationa Staging System, PIs, Protheasome Inhibitors, *IMids* Immunomodulatory Drugs, MoAbs, Monoclonal Antibodies

LOT group ($p<0.001$). Among all patients who reached a CR (115), taking into consideration patients who received autologous stem cell transplantation before KRd treatment (212/316ASCT-evaluable patients, 67%), there was no significant difference between transplanted patients who obtained a CR (80 patients, 38%) during KRD treatment compared with non transplanted patients (104/316 ASCT-evaluable patients, 33%)who obtained a CR (35 patients, 34%) ($p=0.4$).

Not significant difference was seen between patients with extramedullary disease, with 18 patients obtaining a CR(17% of all patients who reached the CR) vs. 27 with <CR(14% of all patients with <CR) ($p=0.6$), or in dialysis (6 patients with CR, 2.6% vs. 5 with <CR, 2.6%) ($p=0.2$).

The mPFS was 23.1 months (CI 20.11–28.62) and mOSwas 62.85 months (CI 53.75–70.34) in the general population (Figs. 1). We also evaluated PFS and OS at 1, 2 and 5 years from the first administration of therapy. Considering the entire population of 356 patients, the PFS was 68.6% at 1 year, 48.7% at 2 years and 21.5% at 5 years (Fig. 1). There was no difference based on age<70 or ≥70 years ($p=0.55$). A significant difference was seen based on the number of prior LOT. Patients with <3 prior LOT had a mPFS of 79.1%, 55.7% and 38.7% at 1, 2 and 5 years respectively vs. 58.8%, 18.6% and 7.41% in patients with ≥3 prior LOT ($p<0.0001$) (Fig. 2). Patients who obtained a CR during treatment had a better mPFS with 92.9%, 54.7% and 33% at 1, 2 and 5 years vs. 54.5%, 22.7% and 14.4% of patients with <CR (Fig. 3). Similar results were observed for patients who reached an ORR vs. patients with <PR: the first group obtained a mPFS at 1, 2 and 5 years of 78.7%, 39.8% and 24.6% respectively vs. 12%, 6% and 0% of those with <PR ($p<0.001$).

Considering the same time points, the median OS was 84.1%, 71.3% and 53.7% respectively in the general population (Fig. 1). There was no difference based on age<70 or ≥70 years ($p=0.67$). Even with regards to the mOS, a significant difference was seen based on the number of LOT. Patients with <3 prior LOT had a mOS of 87.8%, 77.2% and 63.9% at 1, 2 and 5 years respectively vs. patients with ≥3 prior LOT who had a mOS of 80%, 66% and 44.7% ($p=0.0037$) (Fig. 2).

We also performed a landmark analysis of PFS and OS at 1 and 3 years from the end of the 18th cycle of treatment evaluating two groups: those evaluable patients who regularly completed 18 cycles of KRd going on with only lenalidomide and dexamethasone (30 patients), and those who prolonged carfilzomibover the 18th cycle (101 patients). In the secondgroup, the median number of KRd cycles administered was 30(range 19–83). No significant difference in patients' characteristics was found, but it's important to highlight the higher number of patients in ISS III and R-ISS III stage in the cKRd group vs. fixed group (40% vs. 22% for ISS stage and 27% vs. 0% for R-ISS stage, respectively), even if the difference was not significant ($p=0.3$ and 0.2 respectively). (Table 2). After a median follow-up of 48.59 months (CI 27.24–61.24), the mPFS and mOS were not statistically different between the two groups, with PFS 74% and 49% at 1 and 3 years respectively for patients who continued carfilzomib therapy and 78% and 37% for patients who interrupted at 18th cycle ($p=0.34$); the OS was 95.6% and 78.8% vs. 96% and 86.2% at the same timepoints for the two groups (Fig. 4). No additional toxicities were seen in patients who prolonged carfilzomib treatment. The rates of CR and ORR were comparable between cKRd vs. fixed time KRd, with a CR of 62% vs. 68% and ORR of 99% vs. 96% respectively (Table 2).

Discussion

In this survey we evaluated safety and efficacy of KRd treatment in RRMM patients treated in 20 EMN Italian centers outside of clinical trials; we also evaluated the feasibility, safety and efficacy of treatment with fixed or continuous KRd.This is the first real-world series exploring safety and efficacy of continuous KRd regimen. Despite the limitations arising from a retrospective series, including selection bias and missing data, our results highlight the safety of long-term administration of carfilzomib.

The ASPIRE trial demonstrated the efficacy and safety of KRd triplet in RRMM patients. Per protocol, carfilzomib was stopped after 18 cycles because of the limited long-term safety data available when ASPIRE was initiated, whereas

Table 2 Adverse events

Type of toxicity	Overall $N=355$	>18 cycles $N=101$	18 cycles $N=254$	p-value[1]
Hypertension, n (%)				0.2
>2	1 (0.3%)	0 (0%)	1 (0.4%)	
1–2	25 (7.0%)	11 (11%)	14 (5.6%)	
0	329 (93%)	92 (89%)	237 (94%)	
Infections, n (%)				0.2
>2	21 (5.9%)	7 (6.8%)	14 (5.6%)	
1–2	61 (17%)	23 (22%)	38 (15%)	
0	273 (77%)	73 (71%)	200 (79%)	
Neuropathy, n (%)				**0.025**
>2	5 (1.4%)	3 (2.9%)	2 (0.8%)	
1–2	20 (5.6%)	10 (9.7%)	10 (4.0%)	
0	330 (93%)	90 (87%)	240 (95%)	
Anemia, n (%)				0.2
>2	9 (2.5%)	5 (4.9%)	4 (1.6%)	
1–2	32 (9.0%)	7 (6.8%)	25 (9.9%)	
0	314 (88%)	91 (88%)	223 (88%)	
Gastrointestinal, n (%)				**0.027**
>2	10 (2.8%)	2 (1.9%)	8 (3.2%)	
1–2	43 (12%)	20 (19%)	23 (9.1%)	
0	302 (85%)	81 (79%)	221 (88%)	
Cutaneous, n (%)				0.2
>2	7 (2.0%)	2 (1.9%)	5 (2.0%)	
1–2	14 (3.9%)	7 (6.8%)	7 (2.8%)	
0	334 (94%)	94 (91%)	240 (95%)	
Thrombocytopenia, n (%)				0.3
>2	32 (9.0%)	13 (13%)	19 (7.5%)	
1–2	26 (7.3%)	8 (7.8%)	18 (7.1%)	
0	297 (84%)	82 (80%)	215 (85%)	
Pneumonia, n (%)				>0.9
>2	24 (6.8%)	7 (6.8%)	17 (6.7%)	
1–2	18 (5.1%)	5 (4.9%)	13 (5.2%)	
0	313 (88%)	91 (88%)	222 (88%)	
Neutropenia, n (%)				**0.031**
>2	55 (15%)	19 (18%)	36 (14%)	
1–2	19 (5.4%)	10 (9.7%)	9 (3.6%)	
0	281 (79%)	74 (72%)	207 (82%)	
Vascular (thrombosis, phlebitis), n (%)				>0.9
>2	9 (2.5%)	2 (1.9%)	7 (2.8%)	
1–2	20 (5.6%)	5 (4.9%)	15 (6.0%)	
0	326 (92%)	96 (93%)	230 (91%)	
Asthenia, n (%)				>0.9
>2	0 (0%)	0 (0%)	0 (0%)	
1–2	17 (4.8%)	5 (4.9%)	12 (4.8%)	
0	338 (95%)	98 (95%)	240 (95%)	
Osteoarticular, n (%)				>0.9
>2	0 (0%)	0 (0%)	0 (0%)	
1–2	6 (1.7%)	2 (1.9%)	4 (1.6%)	
0	349 (98%)	101 (98%)	248 (98%)	
Renal failure, n (%)				0.6
>2	6 (1.7%)	2 (1.9%)	4 (1.6%)	
1–2	6 (1.7%)	3 (2.9%)	3 (1.2%)	
0	343 (97%)	98 (95%)	245 (97%)	
Cardiovascular, n (%)				0.7
>2	11 (3.1%)	2 (1.9%)	9 (3.6%)	

Table 2 (continued)

Type of toxicity	Overall *N*=355	>18 cycles *N*=101	18 cycles *N*=254	*p*-value[1]
1–2	8 (2.3%)	3 (2.9%)	5 (2.0%)	
0	336 (95%)	98 (95%)	238 (94%)	
Glicometabolic, n (%)				>0.9
>2	0 (0%)	0 (0%)	0 (0%)	
1–2	3 (0.8%)	1 (1.0%)	2 (0.8%)	
0	352 (99%)	102 (99%)	250 (99%)	
Others, n (%)				0.12
>2	5 (1.4%)	3 (2.9%)	2 (0.8%)	
1–2	6 (1.7%)	3 (2.9%)	3 (1.2%)	
0	344 (97%)	97 (94%)	247 (98%)	

[1]Fisher's exact test; Pearson's Chi-squared test

lenalidomide and dexamethasone were continued until progression or unacceptable side effects.(18)ASPIRE trial showeda mOS of 48.3 months and a mPFS of 26.1 months. The 3-year and the 5-year PFS were respectively 38.2% and 25.6%. The ORR was 87.1% with CR of 31.8%. The incidence of AEs was 87% and grade ≥3 AEs were 65.3%; among them, the most common were hematological toxicities, pneumonia and hypertension [5, 6, 21]. Although carfilzomib may exhibit a variety of cardiovascular AEs, we observed (17)hypertension in 26 (7.3%) patients with only 0.3% grade 3–4,cardiovascular events were seen in 19 (5.4%) patients with only 3.1% grade 3–4 and vascular events (thrombosis, thrombophlebitis) were seen in 29 (8%) patients with only 2.5% grade 3–4. We can hypothesize that this observed low cardiovascular toxicity is due topatients' evaluation before treatment, early diagnosis of toxicity andagoodmanagement of cardiovascular and vascular toxicity.

In this real-life survey, we analyzed data of 356 patients treated in 20 Italian centers. 30 of these patients (19)were treated as the ASPIRE schedule with 18 cycles followed by lenalidomide and dexamethasone administration alone; 101 patients were instead treated with continuous triplet therapy until progression or intolerance. In this survey we observed an ORR of 83% with CR in 35%considering the entire population. These data are not much different from the ASPIRE, taking in account the impossibility to compare a clinical trial with a retrospective real-life survey.

Indeed, in the real-life experiences published worldwide[24– [32]], KRd is safe and manageable, achieving ORR up to 95%[29] also in patients with less favourable disease characteristics than ASPIRE cohort at baseline, such as high-risk cytogenetics, or estimated glomerular filtration rate (eGFR)<30 ml/min[24, 28].

Our survey confirms previous observations arising from ASPIRE trial and real-life settings. Prolonged PFS and OS are achieved in patients who had received<2 prior LOT, and achieved at least CR by first year, confirming the utility of the administration of the KRd regimen in the first or second relapse to maximize clinical benefit. Consequentially, patients with <3 prior LOT received a higher median number of KRd cycles (17) vs. patients with ≥3 prior LOT (10) ($p=0.001$). Patients who do not achieve at 1 year at least a PR have a high probability of relapse in the following months.

Differently from other smaller Italian experiences [6, 24–26, 28]or a large Asian experience [30],we could not confirm a significant advantage in patients who had received previous ASCT.

On the contrary we did not observe an inferior outcome in patients with compromised kidney function (eGFR<30 mL/min or requiring dialysis) or extramedullary disease, showing the efficacy of the cKRd in a poor setting of RRMM patients.

Our study has a longer follow-up period compared to the other studies [6, 24–32] on the efficacy of cKRdin patients with a previous renal damage, without significant worsening of the same during therapy, and in patients with extramedullary disease.

Finally, we investigated the efficacy of KRd at fixed timepoints of 1, 2 and 5 years. The PFS in our population was 68.6% (CI 63.9–73.7), 48.7% (CI 43.6–54.4) and 21.5% (CI 16.9–27.3) at these time-points. In the ASPIRE the mPFS was 26.1 months and the 3-year and the 5-year PFS were respectively 38.2% and 25.6%; it means that our data are substantially similar to those of the study in terms of PFS. Instead, the mOS was 48.3 months in the ASPIRE vs. 62.85 months of our survey with more than half patients alive after 5 years from the beginning of treatment. It is likely that this improvement in OS depends on the more recent availability of more effective new drugs that were not presents at the time of the ASPIRE study [2]– [3, 33]– [34]. In the last years many drugs have been introduced into the clinical practice, expecially in the relapsed/refractory setting; these

Table 3 Patients' characteristics of fixed and continuous KRd groups (18 or > 18)

		KRD cycles		
Characteristic	**Overall**, *N* = 131	**>18 cycles**, *N* = 101	**18 cycles**, *N* = 30	**p-value**[1]
Sex, n (%)				0.7
Male	70 (53%)	53 (52%)	17 (57%)	
Female	61 (47%)	48 (48%)	13 (43%)	
Age, median (range)	64 (34, 81)	64 (34, 81)	64 (42, 78)	0.6
Age (70), n (%)				0.8
> 70ys	33 (25%)	26 (26%)	7 (23%)	
≤70ys	98 (75%)	75 (74%)	23 (77%)	
ISS at diagnosis, n (%)				0.3
I	36 (33%)	26 (31%)	10 (43%)	
II	33 (31%)	25 (29%)	8 (35%)	
III	39 (36%)	34 (40%)	5 (22%)	
Unknown	23	16	7	
r-ISS at diagnosis, n (%)				0.2
I	15 (28%)	11 (24%)	4 (44%)	
II	27 (50%)	22 (49%)	5 (56%)	
III	12 (22%)	12 (27%)	0 (0%)	
Unknown	77	56	21	
Autologous, n (%)	88 (69%)	65 (66%)	23 (82%)	0.095
Unknown	4	2	2	
Patients in Dialysis, n (%)	5 (4.0%)	4 (4.1%)	1 (3.8%)	>0.9
Unknown	7	3	4	
Extramedullary disease, n (%)	14 (11%)	10 (10%)	4 (15%)	0.5
Unknown	8	5	3	
IMWG Best Response, n (%)				0.5
sCR	18 (16%)	13 (15%)	5 (19%)	
CR	51 (45%)	39 (44%)	12 (46%)	
nCR	2 (1.8%)	2 (2.3%)	0 (0%)	
VGPR	29 (25%)	23 (26%)	6 (23%)	
PR	10 (8.8%)	9 (10%)	1 (3.8%)	
MR	1 (0.9%)	1 (1.1%)	0 (0%)	
SD	1 (0.9%)	0 (0%)	1 (3.8%)	
PD	0 (0%)	0 (0%)	0 (0%)	
Death	0 (0%)	0 (0%)	0 (0%)	
Not evaluable	2 (1.8%)	1 (1.1%)	1 (3.8%)	
Unknown	17	13	4	
CR, n (%)				0.6
CR	71 (63%)	54 (62%)	17 (68%)	
No CR	41 (37%)	33 (38%)	8 (32%)	
Unknown	19	14	5	
ORR, n (%)				0.4
ORR	110 (98%)	86 (99%)	24 (96%)	
No ORR	2 (1.8%)	1 (1.1%)	1 (4.0%)	
Unknown	19	14	5	
Number of Previous Therapy lines (3), n (%)				0.9
< 3 lines	73 (57%)	57 (57%)	16 (55%)	
≥3 lines	56 (43%)	43 (43%)	13 (45%)	
Unknown	2	1	1	
Number of Previous Therapy lines (5), n (%)				**0.009**
< 5 lines	113 (88%)	92 (92%)	21 (72%)	
≥5 lines	16 (12%)	8 (8.0%)	8 (28%)	
Unknown	2	1	1	

[1]Pearson's Chi-squared test, Wilcoxon rank sum test, Fisher's exact test. *ISS* Internationa Staging System *R-ISS* Revised-Internationa Staging System, *IMWG* International Myeloma Working Group, *sCR* stringent Complete Response, *CR* Complete Response, *VGPR* Very Good Partial Response, *PR* Partial Response, *MR* Minimal Response, *PD* Progressive Disease, *ORR* Overall Response Rate

1 Years	2 Years	5 Years
68.6% (63.9%, 73.7%)	48.7% (43.6%, 54.4%)	21.5% (16.9%, 27.3%)

1 Years	2 Years	5 Years
84.1% (80.3%, 88.0%)	71.3% (66.6%, 76.3%)	53.7% (47.8%, 60.4%)

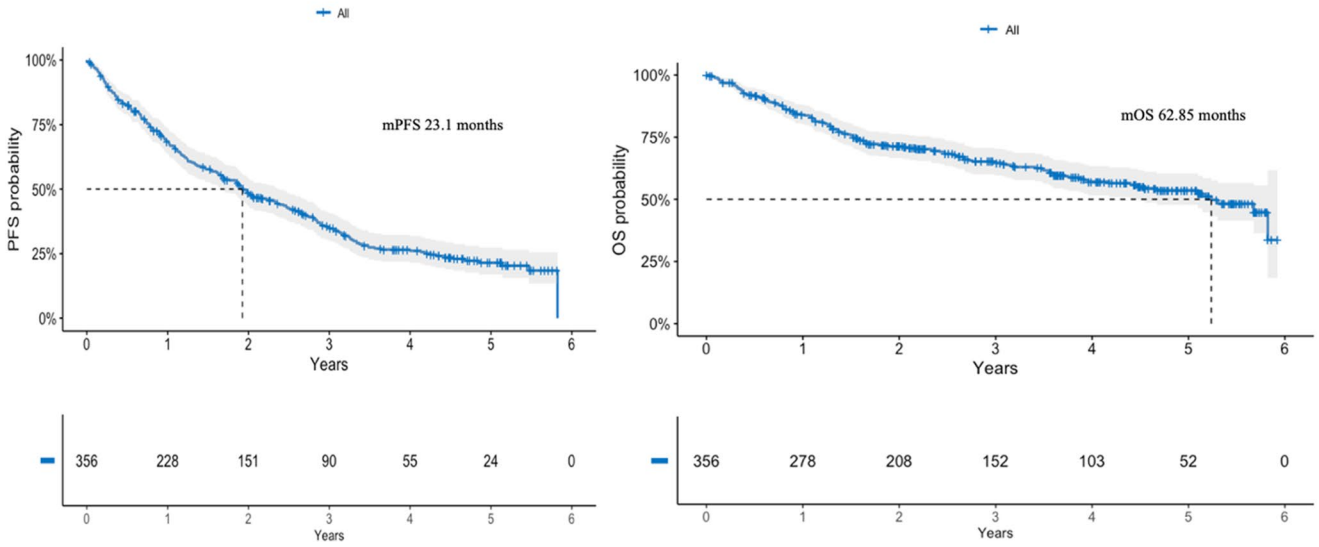


Fig. 1 PFS and OS of the population

	1 Year	3 Years	5 Years
Number of Therapy lines			
< 3 lines	79.1%	55.7%	38.7%
≥ 3 lines	58.8%	18.6%	7.41%

	1 Year	2 Years	5 Years
Number of Therapy lines			
< 3 lines	87.8%	77.2%	63.9%
≥ 3 lines	80.8%	66.0%	44.7%

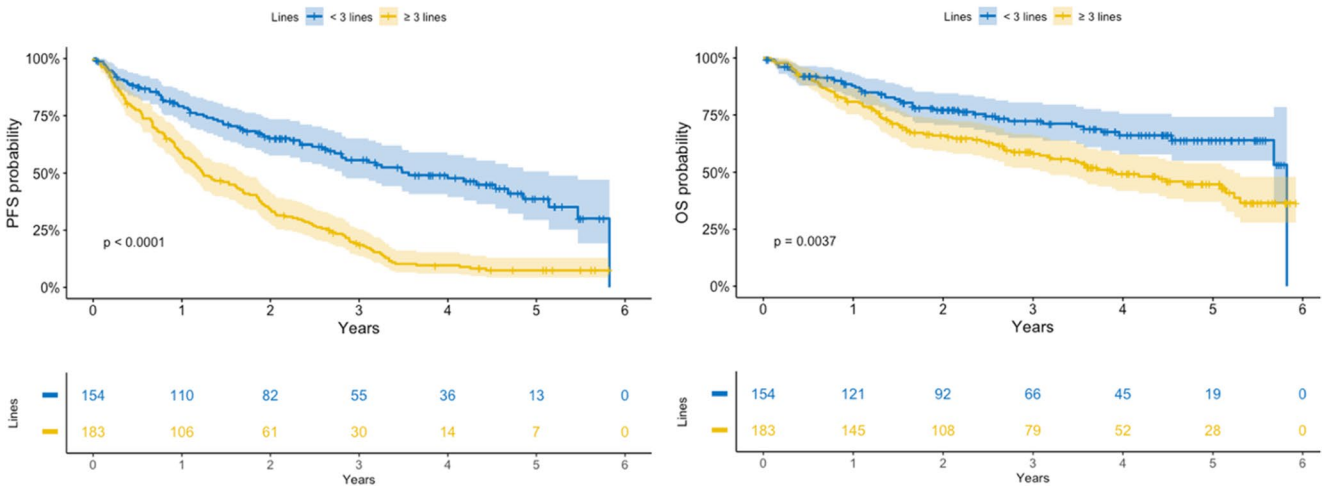
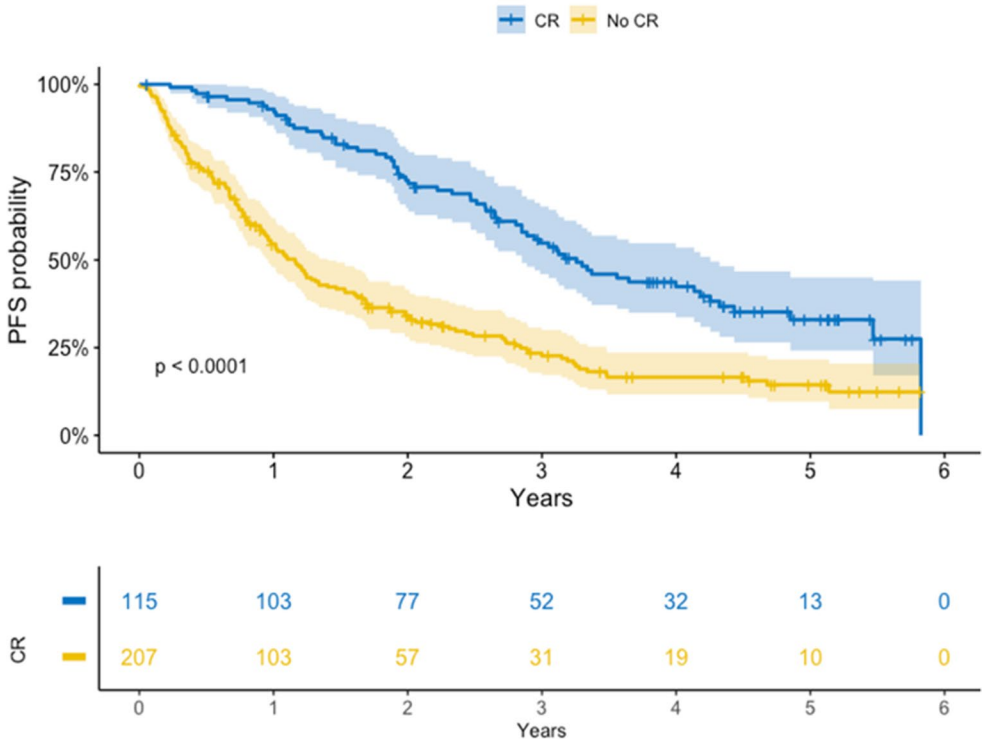
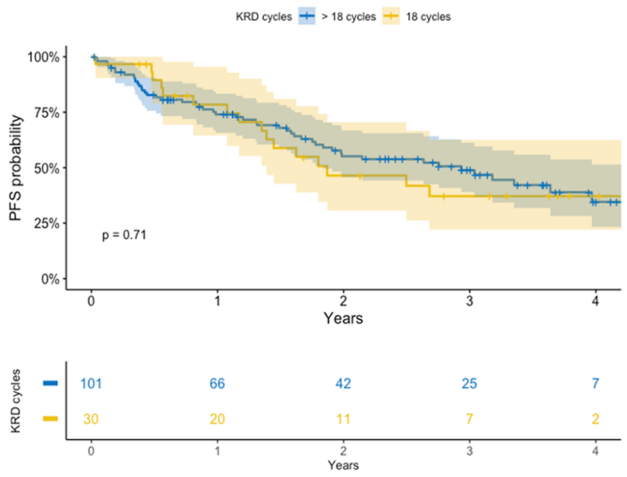


Fig. 2 PFS and OS by therapy lines

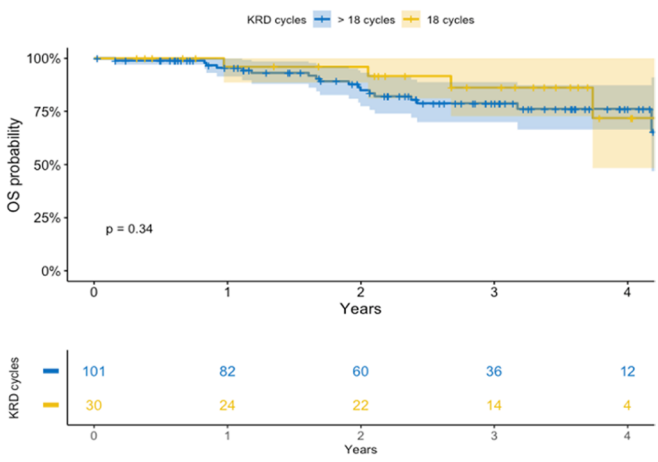
Fig. 3 PFS by achievement of CR

	1 Year	3 Years	5 Years
CR	92.9%	54.7%	33.0%
No CR	54.5%	22.7%	14.4%





	1 Years	3 Years
> 18 cycles	74.0%	48.9%
18 cycles	78.4%	37.2%



	1 Years	3 Years
> 18 cycles	95.6%	78.8%
18 cycles	96.0%	86.2%

Fig. 4 PFS and OS: Landmark analysis from month 18

new therapies have probably contributed to the prolongation of survival of patients relapsed after KRd treatment, and it could explain the prolonged survival in our analyses compared to ASPIRE trial.Similarly, the final analysis of A.R.R.O.W.2 phase 3 has shown that the triplet KRd, even if administered using a different schedule (once-weekly KRd56 or twice-weekly KRd27) can achieve a 12-months mPFS of about 80% [35].

The novelty of our survey is the comparison between continuous carfilzomib beyond 18th cycle compared to fixed carfilzomib with continuous lenalidomide as per ASPIRE trial.We could evaluate data of 30 patients who stopped KRd at 18 cycles and kept on treatment with Rd alone and 101 patients who extended KRd therapy beyond. The landmark analysis of the PFS at 1 year, showed no difference between the two groups, while at 3 years there is a small, not significant advantage in the group of cKRd, even if the cKRd group was enriched of patients with most clinical aggressive disease, as assessed by the difference in the number of patients in ISS and R-ISS stage III.

We can therefore hypothesize that cKRd is able to recover patients with more aggressive disease.

Despite the retrospective nature of this real-life study and lack of a randomization(the decision was made based on the physicians' choice of each center, influenced by the personal experience, at the beginning or during treatment), our landmark analysis shows the feasibility of cKRd, withmanageable toxicities. One of the most common AE was gastrointestinal toxicity, with diarrhea predominantly caused by lenalidomide; the clinical manifestations were represented by 1–2 diarrhea episodes nearly every day. Some patients well tolerated these adverse events, others required a medical intervention due to a perceived reduction in quality of life. Most of these patients were treated with intestinal motility regulators and, when it was not sufficient, by reducing the dosage of lenalidomide. Neuropathy was characterized by reduced sensitivity expecially in the hands; it was primarily grade 1–2 and treated with neurotrophic agents, with some benefit. In cases of grade 3 or persistent grade 2 toxicity, lenalidomide dose was reduced. Extending treatment beyond cycle 18 did not lead to an increase in grade 3–4 AEs, but only a slight increase in grade 1–2 for gastrointestinal toxicity and neuropathy.

Our data confirm the known efficacy of fixed (1) KRd treatment and, after a long-term follow-up, that a prolonged administration of KRD compared to the conventional schedule, although not improving outcomes in RRMM, obtained-consistent results in patients with more aggressive disease profile (ISS III, R-ISS III). Overall, the administration of cKRd was safe and, overall, the toxicity was manageable in both groups of patients.

Conclusions

KRd schedule is a reasonable option especially for second-line treatment. Continuous treatment beyond cycle 18 with lenalidomide or lenalidomide and carfilzomib is safe and manageable. Adding carfilzomib beyond cycle 18, as performed in part of our population, is associated with a slight increase in grade 1–2 for gastrointestinal toxicity and neuropathy, and does not appear to improve clinical benefit; however without a controlled comparison, it is difficult to draw firm conclusions.Our data suggest that cKRd may be considered a valid option for patients with more aggressive disease. However, this hypothesis needs to be confirmed in future further investigations.

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Data availability All data supporting the findings of this study are available from the corresponding author upon request.

Declarations

Competing interests The authors declare no competing interests.

Ethics approval The study was approved bythe independent ethics committee of the coordinating center (n.34/2019/PO). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2024. Informed consent for data processing was obtained from all patients. Carfilzomib-lenalidomide based treatments were performed according to current clinical practice at local institutions.

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