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RESEARCH ARTICLE

Real-world experience of novel multiple myeloma treatments in a large, single-center cohort in Finland

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Abstract

In this single-center study, we aimed to describe the characteristics, treatment patterns, and outcomes of patients with multiple myeloma (MM) following treatment with bortezomib, carfilzomib, daratumumab, ixazomib, lenalidomide or pomalidomide-based regimens. Data were collected retrospectively from a study cohort of patients receiving a MM treatment in the Hospital District of Helsinki and Uusimaa (HUS) in Finland between 2016–2020. In total, 472 patients were included in the study. Median age was 68.2 years and nearly 25% had a high cytogenetic risk according to the International Myeloma Working Group categorization. In 2018–2020, the spectrum of regimens used as third- or later-line therapy was notably broader than in 2016–2017. The overall response rates for patients who received the most novel regimens (available $\leq$ 5 years) in second or third line of therapy (n = 67/430) and fourth line or later (n = 78/151) were 53.3% and 25.0%, respectively. In this real-world MM patient cohort, the response rates for these novel agents were lower compared to those reported in clinical trials. Given the higher cytogenetic risk profile and more advanced disease stage at the time when treated with novel agents, patients could have benefited from effective novel therapies earlier in their treatment pathway.

KEYWORDS
carfilzomib, multiple myeloma, novel treatments, treatment-related outcomes

1. What is the NEW aspect of your work? (ONE sentence) This study characterized the treatment of Finnish multiple myeloma patients during the era of most novel therapies (after 2016) and also included information on the cytogenetic risk profile of this real-world population.
2. What is the CENTRAL finding of your work? (ONE sentence) There are clear differences between real-world populations treated with most novel combinations and those of randomized controlled trials (RCTs), which is reflected by the poorer treatment outcomes in the real-world setting.

3. What is (or could be) the SPECIFIC clinical relevance of your work? (ONE sentence) Given the high cytogenetic risk profile and advanced disease stage at the time when treated with novel agents, patients could have benefited from effective novel therapies earlier in their treatment pathway.

1 | INTRODUCTION

Multiple myeloma (MM) is the second most common hematologic malignancy worldwide and approximately 350 to 400 new MM cases are diagnosed in Finland each year [1]. Although the age-adjusted incidence has remained stable, the prevalence is increasing [1, 2]. The average age at diagnosis fluctuates between 65 to 70 years [3]. The overall 5-year survival rate is 54%, but it varies greatly depending on the patient's risk status. The Revised International Staging System (R-ISS) provides a risk/prognosis stratification based on ISS-stage, lactate dehydrogenase, and high-risk cytogenetics [del(17p) and/or t(4;14) and/or t(14;16)] [4]. The 5-year survival rate is 82% for patients with an R-ISS I stage, 62% with a R-ISS II, and 40% with a R-ISS III [3]. The risk stratification by the International Myeloma Working Group (IMWG) is also based on the ISS stage, but takes the patient's age into account and defines high-risk cytogenetics partially differently [del(17p) and/or t(4;14)] [5].

The overall survival (OS) has improved significantly during the last decades, mainly due to developments in autologous stem cell transplants (ASCT) and novel drug treatments. Novel treatment approaches have also led to improved quality of life among MM patients [6–8]. However, despite improved treatment options, MM remains practically incurable with current therapies and is characterized by multiple relapses. MM typically recurs with a more aggressive disease course after each remission, resulting in a shorter duration of response with each successive line of therapy and, eventually, treatment-refractory disease [8].

During the past 20 years, multiple new drugs have been introduced for the treatment of MM in the relapsed and refractory setting (RRMM), of which the most efficacious have been approved after 2015. These include novel proteasome inhibitors (PIs), that is, carfilzomib and ixazomib, and monoclonal antibodies (mAbs), that is, daratumumab, elotuzumab, and isatuximab. The treatment choice in the relapsed setting is based on the patient's performance status, disease characteristics, and prior treatment history. According to the current MM treatment guidelines, most patients (either ASCT eligible or non-eligible) receive lenalidomide as a part of their first-line therapy, and after relapse, a lenalidomide refractory status will dictate the subsequent treatment choice. If the patient is non-lenalidomide refractory, a lenalidomide-based triplet regimen is recommended for nonfrail patients and a doublet regimen for frail patients. For lenalidomide refractory patients, either a PI-, mAb-, or pomalidomide-based treatment with three (for non-frail patients) or two (for frail patients) compounds is chosen [9, 10].

In Finland, local treatment guidelines issued by the Finnish Myeloma Group [10] recommend treating non-frail, newly diagnosed MM patients below 70–75 years of age with triplet induction regimens of bortezomib, lenalidomide and dexamethasone (VRd); or bortezomib, cyclophosphamide, and dexamethasone (VCd) followed by ASCT and, usually, maintenance therapy. The recommended primary treatment options for nonfrail patients under 85 years and ineligible for ASCT are regimens of VRd; lenalidomide with dexamethasone (Rd); and bortezomib, melphalan, and prednisone (VMP). Dose reductions are taken into account based on performance status. A variety of options are available for the first-line treatment and the complexity further increases along subsequent treatment lines [10]. The most recent agents that have gained local access in Finland are carfilzomib (local access at 11/2015), daratumumab (5/2016), pomalidomide (8/2018), ixazomib (11/2018), and isatuximab (6/2020).

The efficacy and safety of the novel treatment combinations have been extensively studied in the relapsed setting in phase III randomized clinical trials [11–20]. As the treatment landscape has become increasingly complex in terms of treatment options, there is currently no comprehensive up-to-date information available on treatment patterns and outcomes with these treatments in the Finnish clinical setting. This study aimed to describe the characteristics, treatment patterns, and outcomes of MM patients treated with novel therapies available in Finland after 2016, namely bortezomib, carfilzomib, daratumumab, ixazomib, lenalidomide, or pomalidomide-based treatment combinations.

2 | MATERIAL AND METHODS

2.1 | Study population and data collection

This retrospective single-center observational study included all adult (age ≥18 years at diagnosis) MM patients (ICD-10: C90.0) treated with carfilzomib, daratumumab, ixazomib, bortezomib, pomalidomide, or lenalidomide-based treatment combinations in the Hospital District of Helsinki and Uusimaa (HUS) between January 1, 2016 and August 1, 2020. Patients were followed up from the first treatment line after January 1, 2016 (index date) until August 1, 2020, death, or loss to follow-up, whichever occurred first. The baseline period covered the time from the first MM diagnosis until the index date, and the number of treatment lines during the baseline period was also captured.

The following patient and disease characteristics were collected: sex, date of birth (age), date of MM diagnosis, beta2-microglobulin

Twitter summary

In this single-center study, we describe the characteristics, treatment patterns, and outcomes of patients with multiple myeloma (MM) following treatment with bortezomib, carfilzomib, daratumumab, ixazomib, lenalidomide or pomalidomide-based regimens. We collected retrospective data from a study cohort of MM patients receiving treatment in the Hospital District of Helsinki and Uusimaa (HUS) in Finland between 2016 and 2020. Altogether, 472 patients were included. Median age was 68.2 years and nearly 25% had a high cytogenetic risk according to the International Myeloma Working Group categorization. In 2018–2020, the spectrum of regimens used as third- or later-line therapy was notably broader than in 2016–2017. The overall response rates for patients who received the most novel regimens (available $\leq$ 5 years) in the second or third line of therapy (n = 67/430) and fourth line or later (n = 78/151) were 53.3% and 25.0%, respectively. We found that the response rates for these novel agents were lower in this real-world MM patient cohort compared to those reported in clinical trials. Given the higher cytogenetic risk profile and more advanced disease stage at the time when treated with novel agents, MM patients could have benefited from effective novel therapies earlier in their treatment pathway.

level (β_2M, mg/l), albumin level (Alb, g/l), cytogenetic profile [high-risk fluorescent in situ hybridization (FISH) anomalies including del(17p), t(4;14), t(14;16), t(14;20), +1q], MM medication use, and stem cell transplantation procedures conducted.

The data were collected from the electronic health records (EHR) of HUS. Data were accessed via a hematological sub-datalake of the HUS Datalake, which contains pseudonymized data from all available hospital systems. The data have been harmonized with the international Observational Medical Outcomes Partnership (OMOP) common data model.

2.2 | Outcome measures

2.2.1 | Patient and disease characteristics

ISS risk group (I–III) was determined based on the criteria of the International Staging System for Multiple Myeloma [21]. IMWG risk group (low, standard, or high) was determined based on the IMWG categorization [5]. IMWG category was defined for those with both ISS stage and FISH results available, with the exception of subjects who had FISH results unavailable but had ISS I and were aged >55. For those patients, the IMWG risk category was determined as standard.

2.2.2 | Treatment lines

Information on MM treatment regimen and start and end dates for all treatment lines were collected. The following explains various criteria used to determine the start of a new line of therapy. Data on the discontinuation of one treatment regimen and the start of another were used to determine a treatment line. However, restarting the same regimen without any other intervening regimens or discontinuation of one drug from a combination of several drugs was not considered as a new line of treatment. The addition or substitution of one or more drugs in a regimen, excluding dexamethasone alone, was considered as a start of a new treatment line. Induction therapy, followed by autologous or allogeneic stem cell transplantation and maintenance therapy following the transplantation, were considered as one line of therapy (named here as ASCT) if the induction and maintenance were given within +/- 7 months from the transplantation.

Treatment regimens were categorized as follows: bortezomib + dexamethasone (Vd); bortezomib triplet regimens (including bortezomib + lenalidomide + dexamethasone [VRd], bortezomib + cyclophosphamide + dexamethasone [VCd], bortezomib + thalidomide + dexamethasone [VTd], and bortezomib + melphalan + prednisolone [VMP]); carfilzomib + dexamethasone (Kd); carfilzomib + lenalidomide + dexamethasone (KRd); daratumumab + bortezomib + dexamethasone (DVd); daratumumab + lenalidomide + dexamethasone (DRd); ixazomib + lenalidomide + dexamethasone (IRd); lenalidomide + dexamethasone (Rd); pomalidomide + dexamethasone (Pd); and pomalidomide triplet regimens [including bortezomib + pomalidomide + dexamethasone (VPd) and pomalidomide + cyclophosphamide + dexamethasone (PCd)]. Other treatment regimens that are not indicated above were categorized as follows: other novel drug combinations (including all other combinations of bortezomib, carfilzomib, daratumumab, elotuzumab, ixazomib, lenalidomide, or pomalidomide than listed above), and non-novel drug combinations (including combinations that did not apply to other categories). Further, DRd, DVd, Kd, KRd, IRd, Pd, and pomalidomide triplet regimens (VPd and PCd) were categorized as "most novel regimens" (being available in Finland for $\leq$ 5 years during the study period).

2.2.3 | Treatment outcomes

Duration of treatment (DoT) was defined as time from the start of a treatment line to discontinuation (without start of a new treatment line), start of the next treatment line, or death. The end of the study period was considered as a censoring event.

Treatment response during a treatment line was defined to be at least a very good partial response (≥VGPR), if a reduction in serum M-component by >90%, or a serum-free light chain (kappa, lambda) difference of >90%, was observed. Partial response (PR) was defined if a reduction of >50% in the M-component, or a >50% difference in the light chain (kappa, lambda) was observed. Overall response

rate (ORR) was defined as the proportion of patients who had PR or better. Response was determined for patients with measurable disease based on the following cut-off values: serum M-component of ≥10 g/L or serum malign light chain of ≥100 mg/L in the beginning of the first treatment line, and serum M-component of ≥5 g/L or serum malign light chain of ≥100 mg/L in the beginning of subsequent treatment lines.

2.3 | Statistical analyses

The primary analyses consisted of descriptive statistics, including mean, median, standard deviation, and 1st and 3rd quartiles (Q1, Q3) for continuous variables and number and proportion (%) for categorical ones.

Treatment lines were illustrated with a Sankey diagram. Time-to-event treatment outcomes were analyzed using the Kaplan–Meier method, including comparisons with the log-rank test.

A missing data category was added and patients with missing data were included in the analyses. For time-varying covariates, the last observed value was carried forward (LOCF-imputation), and in this case, these variables were not considered to be missing. Other types of imputation methods for missing data were not used.

3 | RESULTS

3.1 | Patient and disease characteristics

In total, 472 patients were included in the study (Table 1). The median age at diagnosis was 68.2 years with 43.2% of patients being 70 years or older. A slightly higher proportion of patients were males (51.3%). Of all the patients, 189 (40.0%) received a stem-cell transplant at some time point, and the proportion was significantly higher for patients below 70 years of age (68.7%) than for patients over 70 years (2.5%). Nearly half (49.1%) of patients with an available ISS status had stage II and 31.2% had stage III. Regarding IMWG risk category, 72.5% of patients had a standard risk, and 24.6% had a high risk. One high-risk chromosomal anomaly [including del(17p), t(4;14), t(14;16), t(14;20)] was present in 8.5% of all patients, and 24.8% of patients had only +1q. At least two anomalies [including del(17p), t(4;14), t(14;16), t(14;20), and +1q] were present in 17.4% of patients. The most common (48.9%) high-risk anomaly was +1q.

In an analysis by treatment regimen received in the second or third line (combined; 2–3L), Rd (151/430) and bortezomib triplet regimens (127/430) were most used (Table 2). Altogether, 67 patients received the most novel regimens. Out of these regimens, KRd ($n = 25$) and Kd ($n = 16$) were the most used. Of the patients receiving Kd, 50.0% were in either standard-risk or high-risk groups. The majority of patients treated with KRd were at standard-risk (57.1%) and 35.7% at high-risk. When taking fourth or later treatment lines (4L+) into account, altogether 40 patients received KRd and 35 Kd. The median age of KRd patients was 69.6 years and 72.0 years for Kd, with 19.5% and 29.7% of patients being 75 years or older at the time of carfilzomib initiation, respectively.

3.2 | Treatment patterns over time

Treatment lines are illustrated by regimen and calendar year in Figure 1. During the whole study period, ASCT was the most common treatment regimen in the first line (104 of 322 patients treated in first line [1L]; 32.3%), followed by Vd ($n = 92$; 28.6%) and bortezomib triplet regimens ($n = 68$; 21.1%). In the second line, Rd was the most common regimen (113 of the 282 patients in second-line [2L]; 40.1%), followed by bortezomib triplet regimens ($n = 96$; 34.0%).

The number of patients receiving third line (3L) treatment was 59 and 89, in 2016–2017 and 2018–2020, respectively. The corresponding numbers for 4 L+ therapies were 34 and 117 in 2016–2017 and 2018–2020, respectively. For patients receiving 3L or 4 L+ therapies during 2018–2020, the variety of regimens used was much broader with more frequent use of novel regimens than in 2016–2017. In 2016–2017, regimens used by at least 10 patients in 3L were Rd ($n = 22$; 37.3%), bortezomib triplet regimens ($n = 12$; 20.3%), and non-novel drug combinations ($n = 10$; 16.9%). In 2018–2020, bortezomib triplet regimens ($n = 19$; 21.3%) and Rd ($n = 16$; 18.0%) were still the most frequently used treatments with KRd being used by 11.2% of patients ($n = 10$). In 4L+, the proportion of patients treated with bortezomib triplet regimens decreased from 41.2% to 8.5% between 2016–2017 and 2018–2020, and the proportion of patients treated with non-novel drug combinations from 35.3% to 9.4%, respectively. In 2018–2020, 62.4% ($n = 73$) of the patients treated in 4L+ received the most novel regimens. Among the most novel regimens used in 2018–2020, pomalidomide triplet regimens ($n = 18$; 15.4% of all patients treated in 4L+), KRd ($n = 15$; 12.8%), and Kd ($n = 15$; 12.8%) were the most commonly used. Transitions between treatment lines are illustrated in Figure S1.

3.3 | Treatment outcomes

Due to the small number of patients receiving the most novel regimens, these patients were combined into a single group for the ORR and DoT analyses. Altogether, 67 patients received the most novel regimens in 2–3L, and 78 patients in 4L+. The ORR was 53.3% (24 patients of the 45 patients having response data available) in 2–3L, and 25.0% (16/64) in 4L+ (Table 3). Median DoT was 4.1 months (95% CI: 3.0–7.6) and 2.7 months (1.9–3.6) in 2–3 and 4L+, respectively. Among the most novel regimens, carfilzomib-based regimens were most used in 2–3L (41/67; 61.2%) and 4 L+ (34/78; 43.6%) (Table 3).

Median OS (mOS) from the start of the 1L treatment was 4.1 years (95% CI: 3.9–NA) and decreased significantly in 2–3 and 4L+ ($p < 0.0001$) (Figure 2A). Patients receiving ASCT survived for significantly longer than non-ASCT patients ($p < 0.0001$, median OS not reached vs. 3.8 years) (data not shown). The mOS for the most novel treatments (combined) received in 2–3 and

TABLE 1 Patient characteristics of the study cohort.

Patient characteristics	Age <70 (N = 268)	Age ≥70 (N = 204)	Total (N = 472)
Sex			
Female	124 (46.3%)	106 (52.0%)	230 (48.7%)
Male	144 (53.7%)	98 (48.0%)	242 (51.3%)
ASCT			
Yes	184 (68.7%)	5 (2.5%)	189 (40.0%)
MM diagnosis year			
-2014	102 (38.1%)	37 (18.1%)	139 (29.4%)
2015-2016	68 (25.4%)	54 (26.5%)	122 (25.8%)
2017-2018	63 (23.5%)	75 (36.8%)	138 (29.2%)
2019-2020	35 (13.1%)	38 (18.6%)	73 (15.5%)
Age at diagnosis			
Mean (SD)	60.6 (7.1)	76.6 (4.8)	67.5 (10.0)
Median	62.4	75.5	68.2
Q1, Q3	55.9, 66.3	72.7, 79.5	60.8, 74.5
ISS			
Missing (N)	5	21	26
I	69 (26.2%)	19 (10.4%)	88 (19.7%)
II	125 (47.5%)	94 (51.4%)	219 (49.1%)
III	69 (26.2%)	70 (38.3%)	139 (31.2%)
IMWG risk group			
Missing (N)	120	145	265
Low	6 (4.1%)	0 (0.0%)	6 (2.9%)
Standard	108 (73.0%)	42 (71.2%)	150 (72.5%)
High	34 (23.0%)	17 (28.8%)	51 (24.6%)
del(17p)			
Missing (N)	48	83	131
Positive	46 (20.9%)	30 (24.8%)	76 (22.3%)
t(4;14)			
Missing (N)	142	144	286
Positive	28 (22.2%)	13 (21.7%)	41 (22.0%)
t(14;16)			
Missing (N)	141	147	288
Positive	11 (8.7%)	8 (14.0%)	19 (10.3%)
t(14;20)			
Missing (N)	152	150	302
Positive	7 (6.0%)	4 (7.4%)	11 (6.5%)
+1q			
Missing (N)	22	57	79
Positive	119 (48.4%)	73 (49.7%)	192 (48.9%)
High-risk FISH anomalies*			
0	122 (45.5%)	111 (54.4%)	233 (49.4%)
1	97 (36.2%)	60 (29.4%)	157 (33.3%)
Only +1q	72 (26.9%)	45 (22.1%)	117 (24.8%)
Other than +1q	25 (9.3%)	15 (7.4%)	40 (8.5%)
>1	49 (18.3%)	33 (16.2%)	82 (17.4%)

Abbreviations: ASCT, autologous or allogenic stem cell transplant; FISH, fluorescent in situ hybridization; ISS, risk group by International Staging System for Multiple Myeloma (21); IMWG, risk group by International Myeloma Working Group categorization (22); MM, multiple myeloma. *All patients included in the analysis (including those with missing information in one or more FISH anomaly components). Category 0 includes all patients that are not applicable to other categories.

TABLE 2 Selected variables at treatment lines 2–3 by regimen and overall.

		Novel (N=373)												
		Most novel (N=67)												
	ASCT (N=15)	KRd (N=25)	Kd (N=16)	DVd (N=3)	DRd (N=7)	IRd (N=4)	Pd (N=4)	Pom triplets (N=8)	Vd (N=20)	Bor triplets (N=127)*	Rd (N=151)	Other novel (N=8)	Non-novel (N=42)	Total (N=430)
Age (y), Median (Q1, Q3)	63.4 (57.7, 65.4)	69.4 (59.4, 72.9)	64.1 (59.4, 70.0)	69.7 (60.9, 70.0)	62.8 (56.6, 66.5)	70.6 (62.4, 75.9)	71.84 (68.93, 77.3)	67.7 (63.9, 71.5)	75.9 (70.3, 79.8)	69.6 (64.0, 75.6)	71.9 (64.9, 77.1)	72.2 (63.1, 73.23)	79.8 (72.3, 83.7)	70.5 (64.0, 76.8)
Sex, male (N, %)	8 (53.3%)	10 (40.0%)	10 (62.5%)	1 (33.3%)	5 (71.4%)	2 (50.0%)	0 (0.0%)	4 (50.0%)	8 (40.0%)	63 (49.6%)	84 (55.6%)	4 (50.0%)	26 (61.9%)	225 (52.3%)
ASCT (N, %),	15 (100.0)	13 (52.0%)	13 (81.2%)	2 (66.7%)	7 (100.0)	1 (25.0%)	3 (75.0%)	5 (62.5%)	7 (35.0%)	55 (43.3%)	53 (35.1%)	3 (37.5%)	5 (11.9%)	182 (42.3%)
ISS (N, %)														
Missing	1	0	0	0	0	0	0	0	1	3	4	0	5	14
I	6 (42.9%)	6 (24.0%)	4 (25.0%)	0 (0.0%)	3 (42.9%)	1 (25.0%)	0 (0.0%)	3 (37.5%)	2 (10.5%)	26 (21.0%)	40 (27.2%)	1 (12.5%)	4 (10.8%)	96 (23.1%)
II	4 (28.6%)	14 (56.0%)	6 (37.5%)	2 (66.7%)	3 (42.9%)	3 (75.0%)	4 (100.0)	3 (37.5%)	11 (57.9%)	57 (46.0%)	64 (43.5%)	4 (50.0%)	16 (43.2%)	191 (45.9%)
III	4 (28.6%)	5 (20.0%)	6 (37.5%)	1 (33.3%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	2 (25.0%)	6 (31.6%)	41 (33.1%)	43 (29.3%)	3 (37.5%)	17 (45.9%)	129 (31.0%)
IMWG risk group (N, %)														
Missing	3	11	8	1	0	2	3	3	13	59	82	4	28	217
Low	0 (0.0%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (14.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (4.4%)	1 (1.4%)	0 (0.0%)	1 (7.1%)	7 (3.3%)
Standard	9 (75.0%)	8 (57.1%)	4 (50.0%)	1 (50.0%)	4 (57.1%)	1 (50.0%)	0 (0.0%)	5 (100.0)	5 (71.4%)	46 (67.6%)	54 (78.3%)	2 (50.0%)	8 (57.1%)	147 (69.0%)
High	3 (25.0%)	5 (35.7%)	4 (50.0%)	1 (50.0%)	2 (28.6%)	1 (50.0%)	1 (100.0)	0 (0.0%)	2 (28.6%)	19 (27.9%)	14 (20.3%)	2 (50.0%)	5 (35.7%)	59 (27.7%)

Abbreviations: ISS, risk group by International Staging System for Multiple Myeloma (21); IMWG, risk group by International Myeloma Working Group categorization (22). *Includes 64 lines with VRd, 21 with VMP, 20 with VTd, 15 with VCd, and 7 with other triplets. ASCT, autologous or allogeneic stem cell transplantation (including induction and maintenance treatment); Bor triplets, bortezomib triplet regimens; DVd, daratumumab + bortezomib + dexamethasone; DRd, daratumumab + lenalidomide + dexamethasone; IRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; KRd, carfilzomib + lenalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; Pom triplets, pomalidomide triplet regimens; Rd, lenalidomide + dexamethasone; Vd, bortezomib + dexamethasone; other novel, all other combinations of carfilzomib, daratumumab, elotuzumab, ixazomib, bortezomib, pomalidomide, or lenalidomide than listed above; non-novel, combinations not applicable to other categories.

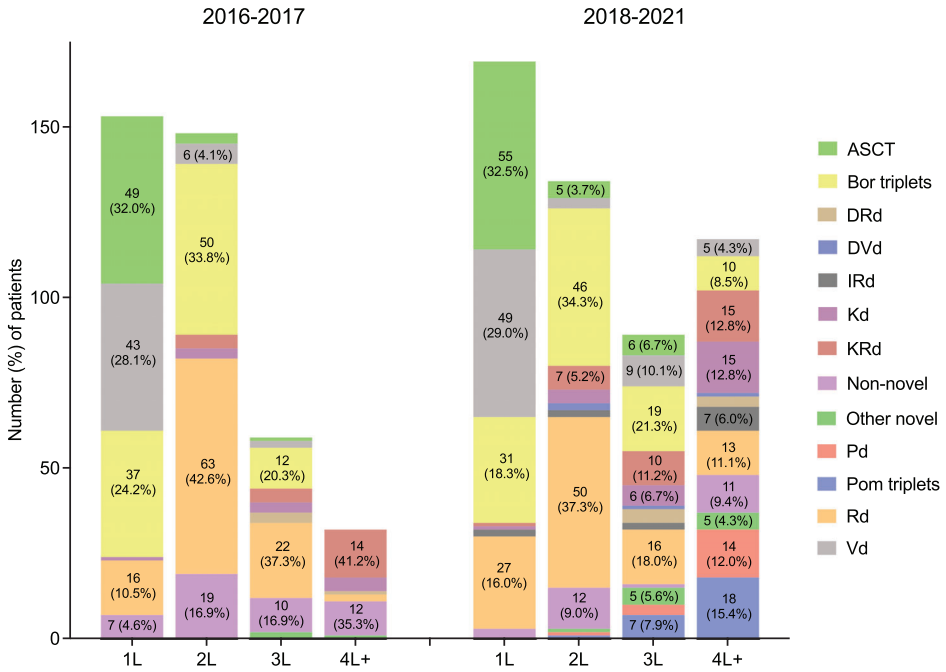

FIGURE 1 Description of treatment lines by regimen and calendar year. ASCT, autologous or allogeneic stem cell transplantation (including induction and maintenance treatment); Bor triplets, bortezomib triplet regimens; DVd, daratumumab + bortezomib + dexamethasone; DRd, daratumumab + lenalidomide + dexamethasone; IRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; KRd, carfilzomib + lenalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; Pom triplets, pomalidomide triplet regimens; Rd, lenalidomide + dexamethasone; Vd, bortezomib + dexamethasone; other novel, all other combinations of carfilzomib, daratumumab, elotuzumab, ixazomib, bortezomib, pomalidomide, or lenalidomide than listed above; non-novel, combinations not applicable to other categories.

TABLE 3 Treatment outcomes of most novel regimens at treatment lines 2–3 and 4+.

	2–3L (N=67)	4L+ (N=78)
Treatment regimens, n (%)		
Kd and KRd	41 (61.2%)	34 (43.6%)
DVd and DRd	10 (14.9%)	5 (6.4%)
IRd	4 (6.0%)	7 (9.0%)
Pd and Pom triplets (VPd, PCd)	12 (17.9%)	32 (41.0%)
Response		
Missing (n)	22	14
ORR, n (%)	24 (53.3%)	16 (25.0%)
PR	17 (37.8%)	10 (15.6%)
>VGPR	7 (15.6%)	6 (9.4%)
DoT, median (95% CI), months	4.1 (3.0–7.6)	2.7 (1.9–3.6)
Prior treatment, n (%)		
IMiDs	44 (65.7%)	75 (96.2%)
PIs	54 (80.6%)	78 (100.0%)

Abbreviations: DoT, duration of treatment; IMiD, immunomodulatory drug; ORR, overall response rate; PI, proteasome inhibitor; PR, partial response; VGPR, very good partial response. DVd, daratumumab + bortezomib + dexamethasone; DRd, daratumumab + lenalidomide + dexamethasone; IRd, ixazomib + lenalidomide + dexamethasone; Kd, carfilzomib + dexamethasone; KRd, carfilzomib + lenalidomide + dexamethasone; Pd, pomalidomide + dexamethasone; Pom triplets, pomalidomide triplet regimen.

4L+ were 1.9 years (1.4–2.5) and 0.7 years (0.4–1.3), respectively (Figure 2B).

4 | DISCUSSION

Several observational studies from Finland on MM capturing data until 2016 have been previously published [2, 22, 23]. This study included patients treated with therapies considered as novel during the study period (2016–2020). The main interest was in the most novel agents that had become available in Finland after 2016.

The patient characteristics of the overall study cohort reflect previous findings from Finland and other European countries with the median age at diagnosis being around 70 years and a slightly higher proportion of patients being male [2, 22–27]. In this study, carfilzomib-based regimens were the most used among the most novel regimens. When comparing the characteristics of the patients treated with carfilzomib-based regimens with those of RCTs, differences can be observed. In our real-world evidence (RWE) cohort, the median age at treatment initiation was 69.6 and 72.0 years for KRd and Kd recipients, respectively. The corresponding figures were 64.0 and 65.0 years in RCT study populations [11, 17]. Of patients receiving Kd in this study, almost 30% were 75 years or older, which is significantly higher than in the ENDEAVOR trial (17%), and in a recent European RWE study (19.6%) [17, 28]. In addition, the proportion of patients having ISS stage II or III (75%) was higher compared to RCT (56%), as well as compared to the European real-world cohort (65.3%) [17, 28].

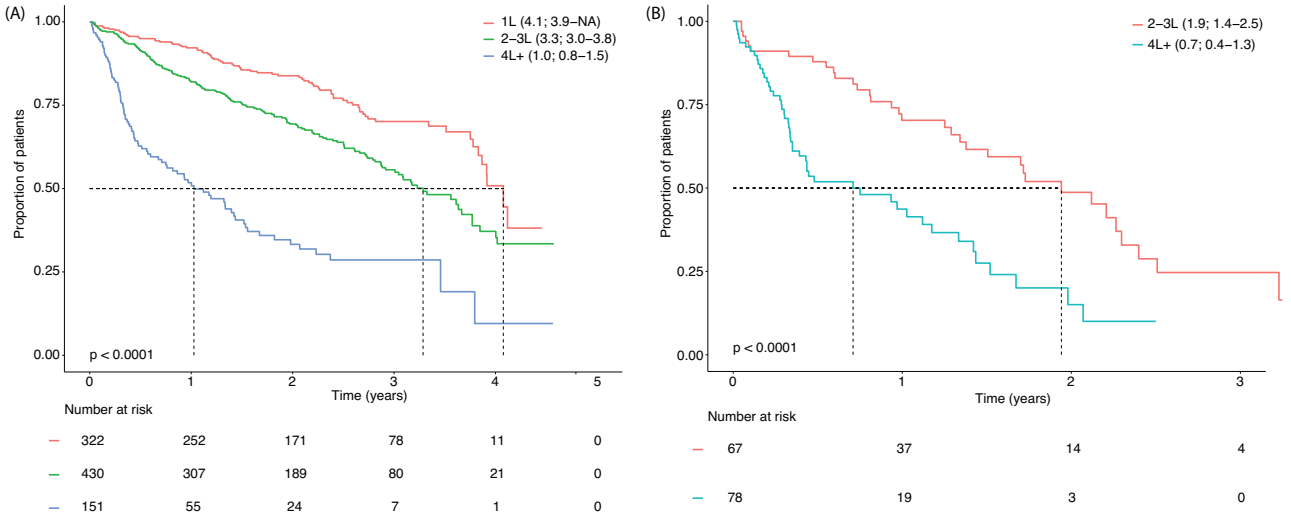

FIGURE 2 Overall survival (in years) by treatment line (1, 2–3, 4+) in the whole study cohort (A), and for the most novel regimens in treatment lines 2–3 and 4+ (B). The value of median survival (95% CI) is shown in parenthesis in the figure legend.

In the large European real-world cohort, the mean age of KRd patients was similar to the RCT population (65.0 and 64.0 years, respectively) and the proportion of patients older than 75 years was 9.6%, which was clearly lower compared to 19.5% seen in this study [11, 29, 30]. In the ASPIRE trial, 12.1% of the KRd patients had high cytogenetic risk, which is in line with the European RWE study (14.6%) but is clearly lower compared to 35.7% observed in our cohort [11, 30]. When compared with other RWE studies, the patient characteristics of KRd patients in the present study were similar to those of two Italian and German studies [27, 31]. In the German study, the median age was 65–72 years and the proportion of patients with ISS stage II or III was 62.5%–80.0% depending on the treatment line. In the German cohort, most of the KRd patients (91.8%) received the combination in the second or third line (vs. 62.5% in the present study) [27].

In recent years, the number of treatment options has increased and the treatment guidelines have been revised several times [9, 10]. Phase II and III trials have demonstrated the efficacy of recently approved agents in the setting of relapsed and/or refractory disease which has especially impacted the treatment practices from the first relapse onward. The prevalence of MM has increased over time due to the expansion of the treatment spectrum with longer survival rates and, consequently, potentially more treatment lines per patient [1]. The findings of this RWE study underline that the proportion of patients in later treatment lines increased between 2016–2017 and 2018–2020. During 2018–2020, the spectrum of different treatment options was clearly larger than during the earlier period.

The comparison of treatment patterns in different populations is difficult for several reasons, for example, the choice of treatment has to be considered with respect to local treatment recommendations and changes in local reimbursement policies [10, 23]. Earlier reports from Europe have shown that most patients receive bortezomib-based regimens in 1L, whereas lenalidomide has been the most commonly used agent in 2L. These observations were based on data between 2014 and 2018, and reflect well the results of the current study from the earlier period (2016–2017) [26, 32]. In contrast, more recent data from Europe showed increasing use of second-generation agents and monoclonal antibodies in the 2L setting [27, 33, 34]. In a real-world cohort from Germany, patients mostly received carfilzomib- or daratumumab-based combinations as 2–3L treatments [27]. Similarly, but with a more modest scale, the emergence of novel treatments was observed in this study during the later time period (2018–2020). In general, the treatment patterns observed in this study are in line with the European and Finnish treatment guidelines prevailing during the study period [9, 10]. Among the most novel drugs, carfilzomib-based combinations were most used in the 2–3L setting (KRd, 25/67 patients receiving most novel treatments; Kd, 16/67), and equally used in 4L+ setting (KRd, 15/78; Kd, 19/78) with Pd (14/78) and pomalidomide triplet regimens (18/78). In the European real-world cohort, the majority of KRd patients were in the first relapse, and more than 50% of patients receiving Kd had at least three prior lines of therapy [28, 30]. In a Finnish RWE study reporting clinical practice between 2005 and 2016, KRd was used from 3L onward in up to 5% of the patients [23]. Taken together, our study showed that the use of the most novel therapies was very limited in Finland between 2016 and 2020. This reflects the policy of well-reasoned uptake of new therapies in Finland and the focus on starting the use of novel treatments from the patient populations with the most difficult-to-treat diseases and the highest unmet medical needs.

A recent Finnish nationwide RWE study showed that the mOS improved by approximately 5 months, from 3.4 years in a cohort that was diagnosed in 2005–2010 to 3.9 years in a cohort that was diagnosed in 2011–2016 ($p = 0.004$) [2]. The investigators concluded that the development was associated with an increase in ASCT frequency, as well as a shift in the ASCT treatment population towards older and more frail subjects. The proportion of patients receiving ASCT increased significantly from 17% in 2005 to 30% in 2015 ($p = 0.002$) [2]. In our cohort, the mOS assessed from the start of the 1L treatment was 4.1 years, showing slight improvement compared to previous

results. Also, a higher proportion of patients (40%) received ASCT in this cohort. Compared to our results showing a mOS of 3.3 years in 2–3L, Touzeau and colleagues showed a mOS of around 2.7 years (32.4 months, 95% CI: 31.2–33.6) from the initiation of 2L therapy in a French cohort of patients receiving novel treatments between 2014 and 2018 [26].

Inherent differences between RWE studies and clinical trials are the heterogeneity of patient populations in the RWE studies and the more rigorous protocols followed in a clinical trial setting. As a result, patient outcomes in the RWE studies may differ from those reported in clinical trials—usually showing inferior outcomes in the real-world setting [35, 36]. Interestingly, Steinmetz and colleagues reported very high ORRs of 90.6%, 84.2%, and 61.3%, in 2L, 3L, and 4L+ settings, respectively, for patients treated with novel treatment regimens between 2017 and 2018 in Germany. We observed significantly poorer response rates (53.3% in 2–3L and 25.0% in 4L+), which could be explained by the significantly larger use of carfilzomib- and daratumumab-based combinations in the German cohort compared with our cohort. As an example, 50.0% and 33.1% of the patients in the German cohort used carfilzomib-based combinations in 2 and 3L, respectively, while the proportion of carfilzomib users was only 9.5% (41/430) in 2–3L in our cohort [27]. In addition, the method used in this study for determining the response was rather crude (see Material and Methods) compared to the detailed assessment of the medical records conducted by the physicians used by Steinmetz and colleagues. This may explain the differences observed between the Finnish and the German cohorts—and certainly with other real-world study designs as well.

There are several recent observational studies focusing on the real-world outcomes of a single treatment regimen. Studies evaluating treatment outcomes of carfilzomib-based combinations have shown lower ORRs compared to those observed in the clinical trial setting, for example, for Kd ranging from 52.9% to 68.8% compared to 77.0% seen in the ENDEAVOR trial [17, 28, 37, 38]. Similarly, clinical performance of daratumumab-based therapies observed in the real-world setting was poor compared with clinical trial data [39]. The higher disease severity and cytogenetic risk profile, together with older age and the use of the studied regimens in later lines of therapy compared to a clinical trial setting, most probably contribute to the inferior treatment outcome results perceived in the observational studies in general. Deeper responses were achieved in earlier lines of therapy, further emphasizing the importance of optimizing treatment sequencing [27, 39]. It is noteworthy that a recent Finnish cohort study reported that the comorbidity burden in the Finnish MM population is high, especially the prevalence of cardiovascular diseases and secondary malignancies, in line with previous observations [40–43]. This further highlights the fact that there are profound differences between the real-world patient populations and those run under strictly controlled clinical trial protocols.

The findings of this study must be considered in the context of existing limitations. Because MM is a rare disease and data from only a single hospital district was used, small subgroups were identified and included in the analysis, especially for the later treatment lines. The data used in retrospective studies reflect the everyday clinical coding practices and thus may be nonstandardized and incomplete. In addition, the rapidly changing treatment landscape and varying coding practices challenge the identification of individual treatment lines, as discussed in connection with earlier studies using similar data sources [2, 22, 23]. Despite these issues, we were able to determine the IMWG risk group and ORR for a subset of patients, which has previously proven to be a challenge in studies utilizing Finnish real-world data. The harmonization of clinical data collected at the HUS hematology department in conjunction with the OMOP initiative at different Finnish University Hospitals offered a more user-friendly interface to the existing data.

5 | CONCLUSION

This RWE study demonstrates that the number of patients in later treatment lines has increased substantially from 2016–2017 to 2018–2020. This reflects the increased number of treatment options and improved survival of patients over time. During recent years, carfilzomib has established its role as a core myeloma treatment and was the most used treatment among the most novel drugs (available for ≤5 years during the study period) in this cohort. Based on the findings of this study, there are clear differences between real-world populations treated with most novel combinations and those of RCTs, which is reflected in treatment outcomes. Even if the patients treated in the real-world setting gain benefit from the increased number of treatment options available, it is still critical to offer the most effective novel therapies to patients early enough in their treatment path to achieve optimal treatment outcomes.

AUTHOR CONTRIBUTIONS

Conception of the work: HL, JM, TY, KS, and JL. *Study design*: HL, JM, TY, KS, and JL. *Acquisition of data*: JM and OB. *Analysis*: JM. *Interpretation*: HL, JM, TY, OB, KP, PK, KS, and JL. *Drafting the manuscript text*: HL. *Revision of the manuscript critically for important intellectual content*: JM, TY, OB, KP, PK, KS, and JL. *Final approval of the version to be published*: All authors. *Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved*: All authors.

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CONFLICT OF INTEREST STATEMENT

HL and JM are employees of MedEngine Oy; TY is the owner of MedEngine Oy; KS is an employee and stockholder at Amgen; OB has received consultancy fees from Novartis and Sanofi, outside the submitted work, and consultancy fees from Amgen, in the submitted work; KP and PK declare no conflict of interest; JL has received consultancy fees from Bristol-Myers Squibb, Sanofi, and Takeda.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available upon request to the corresponding author. The data are not publicly available due to privacy and ethical restrictions.

ETHICS STATEMENT

The study approval was obtained from the Hospital District of Helsinki and Uusimaa (HUS/259/2021) and was performed in accordance with the Declaration of Helsinki and in compliance with applicable national laws.

PATIENT CONSENT STATEMENT

The study was based on existing data, and no interventions were performed. Only secondary data were used, which does not require patient consent according to the Finnish legislation (Act on the Secondary Use of Health and Social Data [552/2019] by the Ministry of Social Affairs and Health).

CLINICAL TRIAL REGISTRATION

The authors have confirmed clinical trial registration is not needed for this submission.

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SUPPORTING INFORMATION

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

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