Short Communication

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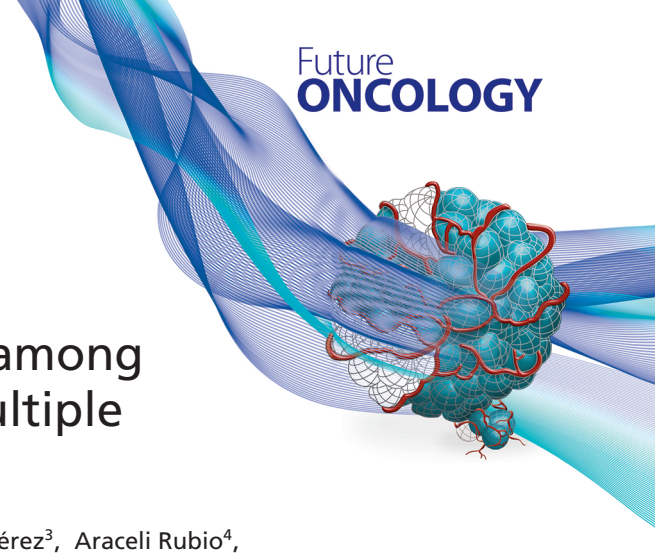

Treatment patterns and outcomes among nontransplant newly diagnosed multiple myeloma patients in Spain

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Aim: To describe treatment patterns and outcomes in nontransplant newly diagnosed multiple myeloma (NDMM) patients in Spain. **Methods:** This retrospective study included two cohorts of NDMM patients diagnosed between 1 January 2012 to 31 December 2013 and 1 April 2016 to 31 March 2017. **Results:** Among 113 patients, proteasome inhibitor (PI) + alkylator combinations (49%) and PI-based regimens without an alkylator (30%) were the most common first-line (1L) therapies. Use of PI + immunomodulatory drug-based regimens increased between the cohorts; PI-based regimens without an alkylator/immunomodulatory drug decreased. Use of 1L oral regimens was low but increased over time; use of maintenance therapy was low across both periods. Median 1L duration of treatment was 6.9 months. **Conclusion:** Short 1L duration of treatment and low use of 1L oral regimens and maintenance therapy highlight unmet needs in NDMM.

Lay abstract: This study describes treatment patterns and outcomes in newly diagnosed multiple myeloma (NDMM) patients in Spain who were not candidates for transplant. The study looked at two patient groups: patients diagnosed between 1 January 2012 and 31 December 2013 and those diagnosed between 1 April 2016 and 31 March 2017. Among the 113 patients considered, the most common first-line therapies were proteasome inhibitor (PI) + alkylator combinations (49%) and PI-based regimens without an alkylator (30%). We saw increased use of PI with immunomodulators (which arm the immune system to battle disease) and decreased use of PI-based regimens without an alkylator or immunomodulator. First-line use of oral regimens was low but increased over time. The median length of first-line treatment for both groups combined was 6.9 months. Finding low use of first-line oral regimens and maintenance therapy and a short duration of first-line treatment, our study highlights the unmet needs that exist in NDMM patients who are not transplant candidates in Spain.

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Keywords: clinical practice patterns • medical records • multiple myeloma • retrospective studies • treatment outcomes

Treatment of multiple myeloma has evolved significantly in the past 15 years, with the approval of the first proteasome inhibitor (PI), bortezomib, in 2004 [1]. Since that time, additional proteasome inhibitors and immunomodulatory agents (IMiDs) have entered the market and been incorporated into practice and clinical guidelines [2]. New drug classes are entering the market, including anti-CD38 antibodies (daratumumab, isatuximab), anti-SLAMF7 monoclonal antibodies (elotuzumab) and less used histone deacetylase inhibitors (panobinostat) and antibody–drug conjugates (belantamab mafodotin) [3–5].

At the time of market authorization, typically only evidence from prospective clinical trials is available for use in clinical decision-making. However, patients recruited to clinical trials of novel treatments are different than patients treated in clinical practice due to strict eligibility criteria employed in clinical trials. It is estimated that 40–75% of MM patients in real-world studies would be ineligible to enter clinical trials due to factors such as advanced age and presence of comorbidities [6–8]. As a result, the risks and benefits of novel therapies demonstrated in real-world studies vary widely from those in clinical trials [9]. Further evaluation of real-world treatment patterns and outcomes will help to quantify the efficacy and effectiveness gap between clinical trial and real-world populations.

We recently completed a retrospective chart review to describe patient characteristics, treatment patterns and outcomes among newly diagnosed multiple myeloma (NDMM) non-stem cell transplant (SCT) patients in a real-world setting in France, Germany, Italy and the UK [10]. The study found differing treatment patterns over time (2012–2013 vs 2016–2017) and across the four countries. PI/alkylator-based regimens were the most commonly prescribed in France, Germany and Italy, but IMiD/alkylator-based regimens were most common in the UK. Use of IMiD)/alkylator regimens decreased in all four study countries between the two periods, while use of PI/alkylator regimens decreased in France and Germany, increased in the UK, and remained stable in Italy. Few patients (5%) received first-line (1L) maintenance therapy. Median first-line duration of therapy (DOT) was 7.0 months and median progression-free survival (PFS) was 32.8 months in the early cohort. As an extension of our previous study conducted in France, Germany, Italy and the UK, we aimed to describe real-world patient characteristics, treatment patterns and outcomes in NDMM non-SCT patients in Spain.

Patients & methods

Study design

Details of the study methods have been reported previously [10]. This was an observational, retrospective chart review study in which physicians or their designees collected data from patient charts using an electronic case report form. Sites were recruited from a list of potential investigators provided by the study sponsor's local affiliates. The study was reviewed and approved by ethics committees at each site.

Selection criteria

Study patients were sampled from two diagnostic periods: the 'early cohort' consists of patients diagnosed between 1 January 2012 and 31 December 2013 and the 'recent cohort' consists of patients diagnosed between 1 April 2016 and 31 March 2017.

Eligible patients were ≥18 years of age at diagnosis; newly diagnosed with active, symptomatic MM; had not undergone frontline SCT; and had at least one of the following myeloma-defining events: ≥60% clonal plasma cells in the bone marrow, an increased level of calcium in the blood, kidney damage, anemia, ≥1 sites of osteolytic bone lesions found on imaging tests, and/or an involved:uninvolved serum FLC ratio ≥100) [11]. In addition, patients were required to have received systemic therapy as the first line of therapy post initial diagnosis and have at least 4 months of follow-up since start of 1L systemic therapy treatment unless the patient died during this period. Patients were excluded if they were enrolled in a clinical trial for 1L systemic therapy or had any prior diagnoses of another malignancy within 5 years of MM diagnosis and evidence of residual disease, except for non-melanoma skin cancer or *in situ* neoplasm.

Study variables

Data were extracted from patient medical charts from the time of MM diagnosis until death or the most recent follow-up. Data elements included demographics and baseline clinical characteristics (e.g., CRAB symptoms, comorbidities, International Staging System (ISS) stage, immunoglobulin class and cytogenetic risk at diagnosis). Also collected were treatment characteristics (including treatment agents, dates of initiation and discontinuation,

plan for determining when to end therapy, reasons for discontinuation), response per International Myeloma Working Group (IMWG) criteria [12] and disease progression according IMWG criteria.

Comorbid conditions were extracted and used to calculate the Charlson Comorbidity Index (CCI) [13]. High cytogenetic risk was defined as presence of del(17p), t(4;14) and/or t(14;16).

First-line medication regimens were categorized based on the route of administration (oral or injectable), number of medications (monotherapy/doublet vs triplet/quadruplet) and drug class (defined below). Medication classes were defined as: IMiDs: lenalidomide, pomalidomide or thalidomide; PIs: bortezomib, carfilzomib or ixazomib; alkylators: melphalan, cyclophosphamide or bendamustine; and steroids: dexamethasone, prednisone, methylprednisolone. Based on this categorization, first-line regimens were described as: PI-based (no IMiD or alkylator as part of the regimen), IMiD-based (no PI or alkylator) alkylator (no PI or IMiD), PI/IMiD combination (no alkylator), PI/alkylator-based (no IMiD), and IMiD/alkylator-based (no PI). Oral regimens included IMiD-based regimens that did not include a PI; regimens including a PI were categorized as injectables, as no patients in the study received the oral PI, ixazomib. Alkylator-based regimens without an IMiD or PI could not be categorized as oral or injectable due to lack of information on route of administration. Medications used as maintenance therapy, defined as therapy received after the induction therapy, but prior to progression, were also extracted. Treatment plan (treatment until progression, fixed DOT or treatment to best response/plateau) and reason for discontinuation were also extracted from the patient medical record.

DOT, time to best response and PFS were calculated using treatment, response and progression dates extracted from patient charts. For these outcomes, the early and recent cohorts were pooled.

Statistical analysis

Differences between the early and recent cohorts were tested using Pearson's Chi-square test or Fisher's exact test for categorical variables and the Student's *t*-test for continuous variables. An alpha level of 0.05 was used for all inferences. Time-to-event outcomes were analyzed using Kaplan-Meier analysis accounting for censoring dependent end points and adjusted for key baseline patient demographic and clinical characteristics, which included age, ethnicity, presence of CRAB symptoms (hypercalcemia, renal failure, anemia, bone involvement), comorbidities, International Staging System (ISS) stage, MM type, immunoglobulin class, ECOG performance status (PS), frailty status and cytogenetic risk at diagnosis (enabling comparisons to the initial publication) [10]. Analyses were conducted using SAS® software, version 9.4.

Results

Patient demographic & clinical characteristics

A total of seven investigators and sites participated in the Spain study. All investigators were public academics and their respective institutions were all teaching hospitals. All investigators worked in the field of hematologic neoplasms.

The sites enrolled 113 patients (early cohort: 65, recent cohort: 48). Median age (overall sample) was 76.0 years at MM diagnosis (early cohort: 77.0; recent cohort: 75.0), with 65.5% being ≥75 years old (early cohort: 70.8%; recent cohort: 58.3%; Table 1). Most patients (overall sample) were female (55.8%), nearly half had ISS stage III (46.9%) and most had a CCI >0 (69.9%).

Cytogenetic testing

Approximately half of patients in the study had cytogenetic testing performed, with the rate of testing not significantly different between the early and recent cohorts (44.6 vs 58.3%; p = 0.149). The percentage of patients with high cytogenetic risk (among those tested) was 24.6% in the overall sample (early cohort: 20.7%, recent cohort: 28.6%).

First-line treatment patterns

The most common 1L regimens were PI/alkylator-based (48.7%), followed by PI-based (30.1%; Table 2). The most common regimen in both cohorts was bortezomib (V) + melphalan (M) ± steroid (early cohort, 46.2%; recent cohort, 41.7%). Use of V ± steroid in 1L decreased from 36.9% in the early cohort to 20.8% in the recent cohort, while use of V + lenalidomide (R) ± steroid increased from 1.5% in the early cohort to 14.6% in the recent cohort. The distribution of 1L medication classes did not differ significantly between patients with high and standard cytogenetic risk (p = 0.640).

Table 1. Baseline patient characteristics by cohort.

Characteristics	All (n = 113)	Early cohort (n = 65)	Recent cohort (n = 48)
Age, n (%):	50 (44.2)	29 (44.6)	21 (43.8)
Median	76	77	75
<65 years	9 (8.0)	4 (6.2)	5 (10.4)
65–74 years	30 (26.5)	15 (23.1)	15 (31.3)
≥75 years	74 (65.5)	46 (70.8)	28 (58.3)
Female, n (%)	63 (55.8)	36 (55.4)	27 (56.3)
ECOG PS, n (%):			
0	6 (5.3)	4 (6.2)	2 (4.2)
1	10 (8.8)	6 (9.2)	4 (8.3)
2	11 (9.7)	7 (10.8)	4 (8.3)
3	5 (4.4)	2 (3.1)	3 (6.3)
4	1 (0.9)	1 (1.5)	0 (0.0)
Unknown	80 (70.8)	45 (69.2)	35 (72.9)
CCI, n (%):			
0	30 (26.5)	16 (24.6)	14 (29.2)
1	31 (27.4)	19 (29.2)	12 (25.0)
≥2	48 (42.5)	29 (44.6)	19 (39.6)
Unknown	4 (3.5)	1 (1.5)	3 (6.3)
ISS stage, n (%):			
Stage I	14 (12.4)	8 (12.3)	6 (12.5)
Stage II	34 (30.1)	16 (24.6)	18 (37.5)
Stage III	53 (46.9)	32 (49.2)	21 (43.8)
Unknown	12 (10.6)	9 (13.8)	3 (6.3)
Immunoglobulin class, n (%):			
IgG	57 (50.4)	32 (49.2)	25 (52.1)
IgA	24 (21.2)	12 (18.5)	12 (25.0)
Light chain only	21 (18.6)	14 (21.5)	7 (14.6)
IgD	1 (0.9)	1 (1.5)	0 (0.0)
Other†	6 (5.3)	3 (4.6)	3 (6.3)
Unknown/not documented	4 (3.5)	3 (4.6)	1 (2.1)
Extramedullary disease, n (%):	14 (12.4)	8 (12.3)	6 (12.5)
CRAB symptoms, n (%):			
Renal insufficiency	18 (15.9)	10 (15.4)	8 (16.7)
Hypercalcemia	9 (8.0)	5 (7.7)	4 (8.3)
Anemia	45 (39.8)	28 (43.1)	17 (35.4)
Bone lesions	57 (50.4)	32 (49.2)	25 (52.1)
Cytogenetic testing done, n (%):	57 (50.4)	29 (44.6)	28 (58.3)
High risk	14 (12.4)	6 (9.2)	8 (16.7)
Standard risk	43 (38.1)	23 (35.4)	20 (41.7)
Unknown risk	56 (49.6)	36 (55.4)	20 (41.7)
Follow-up duration from NDMM diagnosis in months, median (IQR)	31.7 (12.5–40.3)	35.8 (9.7–61.4)	30.9 (21.8–34.9)

†Other Ig class includes Bence Jones/lambda, multi-molecular MM.
CCI: Charlson Comorbidity Index; CRAB: Hypercalcemia, renal insufficiency, anemia, and bone lesions; ECOG PS: Eastern Cooperative Oncology Group Performance status; IQR: Interquartile range; ISS: International staging system.

Overall use of 1L oral regimens was low (4.4%) but increased between the early cohort (1.5%) and recent cohort (8.3%; Table 2). Use of triplet regimens also increased, from 56.9% in the early cohort to 68.7% in the recent cohort. Fifteen percent of patients received post-induction maintenance therapy in 1L, with regimens being a mix of IMiD based, PI based and both IMiD/PI based (Table 2).

Table 2. Regimen type by cohort.

Category	All (n = 113), n (%)	Early cohort (n = 65), n (%)	Recent cohort (n = 48), n (%)
Induction therapy, by mechanism of action			
• PI/alkylator:	55 (48.7)	32 (49.2)	23 (47.9)
VC ± steroid	5 (4.4)	2 (3.1)	3 (6.3)
VM ± steroid	50 (44.2)	30 (46.2)	20 (41.7)
• PI:	34 (30.1)	24 (36.9)	10 (20.8)
V ± steroid	34 (30.1)	24 (36.9)	10 (20.8)
• PI/IMiD:	10 (8.8)	3 (4.6)	7 (14.6)
VR ± steroid	8 (7.1)	1 (1.5)	7 (14.6)
VT ± steroid	2 (1.8)	2 (3.1)	0 (0.0)
• IMiD:	5 (4.4)	1 (1.5)	4 (8.3)
R ± steroid	5 (4.4)	1 (1.5)	4 (8.3)
• Alkylator:	4 (3.5)	3 (4.6)	1 (2.1)
M ± steroid	4 (3.5)	3 (4.6)	1 (2.1)
• Other:	5 (4.4)	2 (3.1)	3 (6.3)
VMR ± steroid	1 (0.9)	0 (0.0)	1 (2.1)
VMC ± steroid	2 (1.8)	1 (1.5)	1 (2.1)
Other	2 (1.8)	1 (1.5)	1 (2.1)
Induction therapy, by number of agents:			
• Doublet or less	43 (38.1)	28 (43.1)	15 (31.3)
• Triplet or more	70 (61.9)	37 (56.9)	33 (68.7)
Induction therapy, by route of administration†:			
• Oral	5 (4.4)	1 (1.5)	4 (8.3)
• Injectables	103 (91.2)	61 (93.8)	42 (87.5)
• Other	5 (4.4)	3 (4.6)	2 (4.2)
Maintenance:	17 (15.0)	9 (13.8)	8 (16.7)
• R ± steroid	5 (29.4)	3 (33.3)	1 (12.5)
• T ± steroid	4 (23.5)	1 (11.1)	3 (37.5)
• V ± steroid	3 (17.6)	3 (33.3)	0 (0.0)
• VR ± steroid	1 (5.9)	0 (0)	1 (12.5)
• Other	4 (23.5)	2 (22.2)	3 (37.5)

†IMiD-based regimens that did not contain a PI were classified as oral regimens, and PI or PI combinations such as PI/IMiD- or PI/alkylator-based regimens were classified as injectables.
C: Cyclophosphamide; IMiD: Immunomodulatory drug; M: Melphalan; PI, proteasome inhibitor; R: Lenalidomide; T: Thalidomide; V: Bortezomib.

Treatment plan

The majority of regimens were planned to continue until best response was achieved (57.5%), followed by treatment until disease progression (23.0%) and treatment for a fixed duration (19.5%; Table 3). More patients in the recent cohort were planned to be treated until disease progression compared with the early cohort (33.3 vs 15.4%; p = 0.047), while more patients in the early cohort were treated for a fixed duration (24.6 vs 12.5%; p = 0.047). As shown in Table 3, PI/alkylator-based combinations were mostly administered until best response.

Reasons for discontinuation

The majority of patients (91.2%) discontinued 1L therapy during the study period. The most common reasons for discontinuation were an adverse event or death (27.4%) and completion of planned treatment (26.5%; Table 4).

Clinical outcomes

In the combined early and recent cohorts, adjusted median 1L DOT was 6.9 months (95% CI: 5.5–8.6 months; Figure 1A). Best 1L response was achieved at a median of 5.8 months (95% CI: 4.5–6.9 months; Figure 1B). Median PFS from start of 1L therapy was 22.5 months (95% CI: 18.1–35.7 months; Figure 1C).

Table 3. First-line treatment plans by cohort.

	All, n (%)	Early cohort, n (%)	Recent cohort, n (%)
All regimens:	n = 113	n = 65	n = 48
To best response	65 (57.5)	39 (60.0)	26 (54.2)
To progression	26 (23.0)	10 (15.4)	16 (33.3)
Fixed duration	22 (19.5)	16 (24.6)	6 (12.5)
PI/alkylator-based:	n = 57	n = 33	n = 24
To best response	39 (68.4)	23 (69.7)	16 (66.7)
To progression	8 (14.0)	3 (9.1)	5 (20.8)
Fixed duration	10 (17.5)	7 (21.2)	3 (12.5)
PI-based:	n = 36	n = 25	n = 11
To best response	17 (47.2)	11 (44.0)	6 (54.5)
To progression	12 (33.3)	7 (28.0)	5 (45.5)
Fixed duration	7 (19.4)	7 (28.0)	0 (0.0)
PI/IMiD-based:	n = 10	n = 3	n = 7
To best response	3 (30)	1 (33)	2 (29)
To progression	2 (20)	0 (0.0)	2 (29)
Fixed duration	5 (50)	2 (67)	3 (43)
IMiD-based:	n = 5	n = 1	n = 4
To best response	2 (40.0)	1 (100.0)	1 (25.0)
To progression	3 (60.0)	0 (0.0)	3 (75.0)
Fixed duration	0 (0.0)	0 (0.0)	0 (0.0)
Alkylator:	n = 4	n = 3	n = 1
To best response	4 (100.0)	3 (100.0)	1 (100.0)
To progression	0 (0.0)	0 (0.0)	0 (0.0)
Fixed duration	0 (0.0)	0 (0.0)	0 (0.0)
Oral:	n = 5	n = 1	n = 4
To best response	2 (40.0)	1 (100.0)	1 (25.0)
To progression	3 (60.0)	0 (0.0)	3 (75.0)
Fixed duration	0 (0)	0 (0.0)	0 (0.0)
Injectable:	n = 103	n = 61	n = 42
To best response	59 (57.3)	35 (57.4)	24 (57.1)
To progression	22 (21.4)	10 (16.4)	12 (28.6)
Fixed duration	22 (21.4)	16 (26.2)	6 (14.3)

Treatment plan of other regimens (n = 2) not listed due to low sample size.
IMiD: Immunomodulatory drug; PI: Protease inhibitor.

Discussion

In this real-world study of NDMM non-SCT patients in Spain, we found that 92% of patients received a first-line treatment regimen containing bortezomib. Specifically, bortezomib + melphalan ± steroid (VMP; 41.5% early, 39.6% recent) was the most common regimen, followed by bortezomib + dexamethasone (Vd; 36.9% early, 18.8% recent). Use of doublet regimens, specifically Vd, decreased between the early and recent cohorts, while use of triplet regimens increased. Treatment patterns in Spain were similar to that in Italy, shown in our previous study, with more use of PI/alkylator-based regimens and less use of IMiD/alkylator-based regimens compared with France, Germany and the UK [10]. However, use of VMP was lower than that reported in a 2014 survey of experts from 41 hospitals in Spain, which indicated that 97% of nontransplant patients received first-line VMP [14]. One possible explanation for a higher use of injectable regimens in Italian and Spanish populations is the influence of GIMEMA and GEM-PETHEMA clinical trials conducted in these countries, showing superior outcomes in patients receiving VTd compared with Td [15,16].

Lenalidomide-containing regimens were prescribed to 3.1% of patients in the early cohort and 25.0% of patients in the recent cohort ($p < 0.001$), primarily driven by an increase in use of bortezomib + lenalidomide ± steroid (VRd) and lenalidomide ± steroid (Rd). Increasing use of Rd likely reflects randomized clinical trials published

Table 4. First-line regimen discontinuation rates and reasons for discontinuation by cohort.

	All	Early	Recent
All regimens:	n = 103	n = 61	n = 42
AE/death	31 (27.4)	19 (29.2)	12 (25.0)
Planned treatment completed	30 (26.5)	18 (27.7)	12 (25.0)
Treatment failure	28 (24.8)	13 (20.0)	15 (31.3)
Remission/maximum clinical benefit achieved	21 (18.6)	14 (21.5)	7 (14.6)
Other	3 (2.7)	1 (1.5)	2 (4.2)
PI/alkylator-based:	n = 57	n = 33	n = 24
AE/death	12 (21.1)	8 (24.2)	4 (16.7)
Planned treatment completed	14 (24.6)	8 (24.2)	6 (25.0)
Treatment failure	16 (28.1)	7 (21.2)	9 (37.5)
Remission/maximum clinical benefit achieved	13 (22.8)	9 (27.3)	4 (16.7)
Other	2 (3.5)	1 (3.0)	1 (4.2)
PI-based:	n = 36	n = 25	n = 11
AE/death	14 (38.9)	8 (32.0)	6 (54.5)
Planned treatment completed	9 (25.0)	8 (32.0)	1 (9.1)
Treatment failure	6 (16.7)	4 (16.0)	2 (18.2)
Remission/maximum clinical benefit achieved	6 (16.7)	5 (20.0)	1 (9.1)
Other	1 (2.8)	0 (0.0)	1 (9.1)
PI/IMiD-based:	n = 10	n = 3	n = 7
AE/death	1 (10.0)	0 (0.0)	1 (14.3)
Planned treatment completed	5 (50.0)	2 (66.7)	3 (42.9)
Treatment failure	3 (30.0)	1 (33.3)	2 (28.6)
Remission/maximum clinical benefit achieved	1 (10.0)	0 (0.0)	1 (14.3)
Other	0 (0.0)	0 (0.0)	0 (0.0)
IMiD-based:	n = 5	n = 1	n = 4
AE/death	2 (40.0)	1 (100.0)	1 (25.0)
Planned treatment completed	1 (20.0)	0 (0.0)	1 (25.0)
Treatment failure	2 (40.0)	0 (0.0)	2 (50.0)
Remission/maximum clinical benefit achieved	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)
Alkylator:	n = 4	n = 3	n = 1
AE/death	2 (50.0)	2 (66.7)	0 (0.0)
Planned treatment completed	0 (0.0)	0 (0.0)	0 (0.0)
Treatment failure	1 (25.0)	1 (33.3)	0 (0.0)
Remission/maximum clinical benefit achieved	1 (25.0)	0 (0.0)	1 (100.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Other regimens (n = 2) not listed due to low sample size.
AE: Adverse event; IMiD: Immunomodulatory drug; PI: Protease inhibitor.

between the diagnosis periods for the early and recent cohorts [17], which drove the addition of Rd as a first-line option in ESMO guidelines [18]. Moreover, the population included in this study represent an older population than other real-world studies, with a median age of 76 years at diagnosis compared with a previous study in Spain in which patients were a median of 69 years at relapse [19]. This may help to explain greater use of Rd, and less use of VMP, in this population, because Rd is associated with a more tolerable safety profile in elderly patients [20].

Use of all-oral regimens was rare (4.4%) but use increased over time (1.5% in the early cohort to 8.3% in the recent cohort), again primarily driven by increased use of Rd. In our previous study, all-oral regimens were used in 16% of patients treated in France, Germany, Italy and the UK; highest in France (25%) and lowest in Italy (6%) [10,15,16]. There is evidence that oral agents are preferred by patients [21], and associated with less economic burden compared with injectable agents [22]. Well-tolerated oral treatments allow for continuous therapy, which has been shown to improve clinical outcomes [22–24]. In a pooled analysis of three Phase III trials in mostly non-SCT

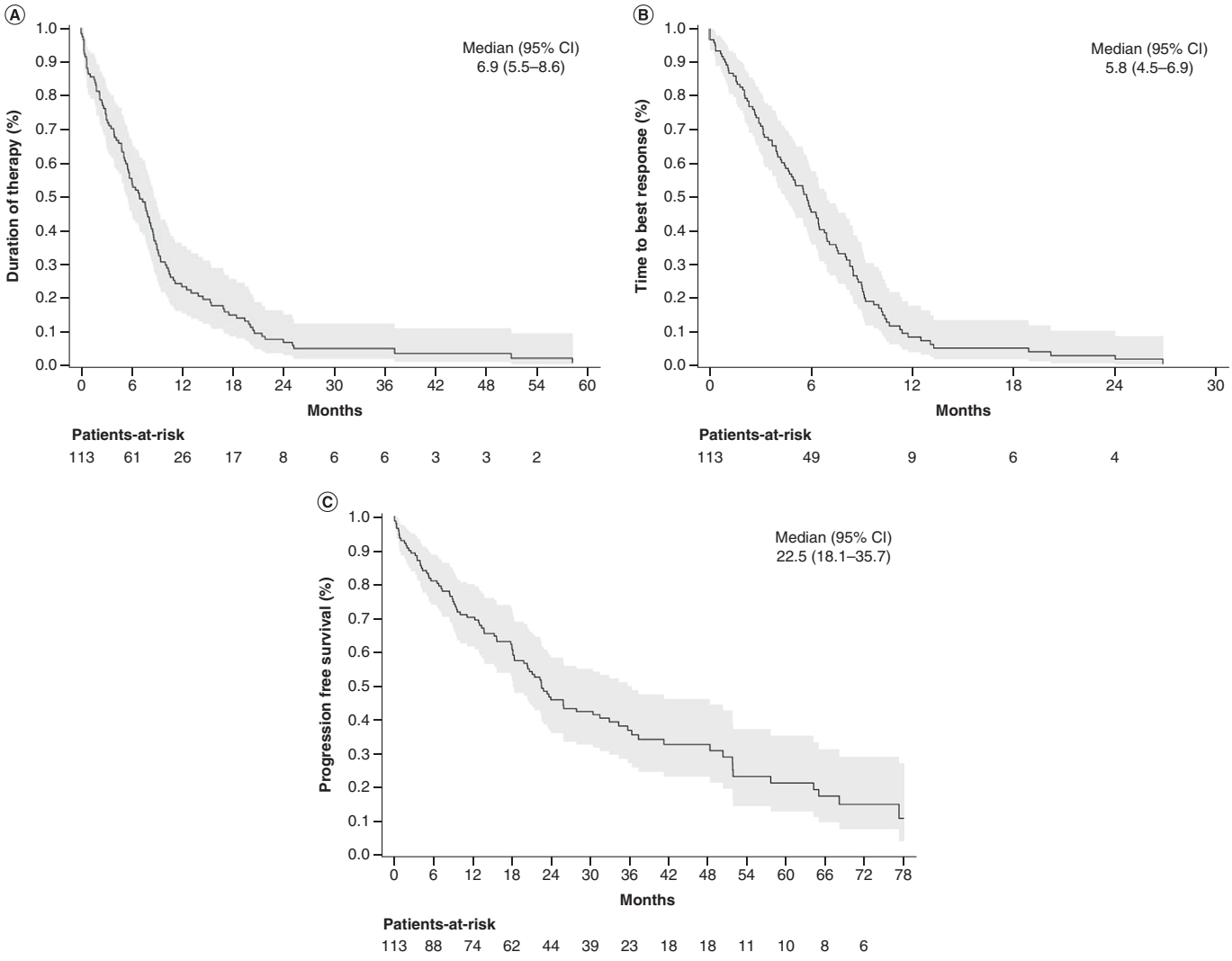

Figure 1. First-line duration of therapy (A), time to best response (B) and progression-free survival (C) in patients in both cohorts.
All analyses were adjusted for age, CRAB symptoms, comorbidities, ethnicity, ISS stage, MM type, immunoglobulin class, ECOG PS, frailty status and cytogenetic risk at diagnosis.

NDMM patients, treatment with thalidomide, lenalidomide or bortezomib improved median PFS (32 months) in patients receiving continuous treatment versus 16 months in patients treated with a fixed duration of therapy ($p < 0.001$), and 4-year OS (69% in patients receiving continuous treatment vs 60% in those treated for a fixed duration, $p = 0.003$) [24]. Use of fixed-duration regimens in this study decreased, while planned treatment until progression increased, in line with current evidence. In our previous study, the median DOT of oral regimens and PFS were significantly longer than those of injectable regimens [10], consistent with other real-world studies indicating favorable PFS (ranging from 11.1–27.6 months) for oral treatments [25,26]. Additional real-world studies comparing oral versus injectable regimens for NDMM patients are needed to confirm the association of a longer DOT with oral regimens versus shorter DOT with injectable regimens and improved clinical outcomes.

Use of cytogenetic testing increased between the early and recent cohorts, and was higher in Spain than in other European countries [10]. Of those tested, nearly a quarter were found to have high cytogenetic risk. Identification of patients with del(17p), t(4;14), and t(14;16) mutations is essential for risk-directed therapy and optimization of patient outcomes [18,27,28]. The use of maintenance therapy in our study was also low, without significant differences between cohorts over time. This is consistent with our previous study in which 5% of NDMM patients in France, Germany, Italy and the UK received maintenance treatment in both cohorts. There are currently no treatments approved for maintenance therapy in non-SCT NDMM by the European Medicines Agency (EMA).

However, the latest evidence supports the use of IMiD or PI-based maintenance therapy to improve PFS and OS in patients who achieve complete response or very good partial response to induction therapy. Orally administered maintenance therapy options are particularly suited for prolonged use due to convenience of administration [29]. Barriers to the implementation of maintenance therapy such as a lack of approval, toxicity, including secondary primary malignancies, cost and impact on the quality of life need to be further investigated [30].

Current (2021) European guidelines recommend the addition of daratumumab to VMP (D-VMP) and Rd (D-Rd) in newly diagnosed patients who are not eligible for ASCT, with daratumumab given continuously until progression [31]. Compared with VMP, D-VMP is associated with longer progression-free survival (hazard ratio [HR], 0.42; 95% CI: 0.34 to 0.51) and overall survival (HR, 0.60; 95% CI: 0.46–0.80) [32]. VRd is also recommended in European guidelines but is not approved for use in Spain.

Strengths & limitations

A key strength of the study is the detailed real-world data collected on treatment characteristics, treatment patterns and clinical outcomes of non-SCT NDMM patients. The population enrolled is similar in baseline characteristics to other chart review studies across Europe, including our initial publication [10]. However, we are unable to rule out that selection bias toward younger, healthier patients with complete data may have impacted clinical outcomes such as PFS. Treatment patterns are representative of the seven sites that participated in the study and may not be representative of treatment approaches at non-enrolled sites. In our previous study, which included France, Germany, Italy and UK, a larger number of sites per country were enrolled (ranging from 10 sites in Italy to 57 sites in Germany) [10], providing a greater diversity of practice patterns across sites. Real-world assessment of disease progression and response may differ from those in a clinical trial setting, given the lack of stringent, protocol-driven frequency of follow-up, disease management and clinical outcome assessment criteria [33]. Finally, the presence of comorbidities and adverse events may be underreported in real-world patient charts.

Conclusion

Uptake of all-oral regimens has been slow in Spain compared with other European countries due to extensive use of PI/alkylator combinations, despite evidence suggesting positive clinical outcomes and lessened economic burden. Although recent data support the use of IMiD- or PI-based maintenance therapy to improve PFS and OS in patients who have achieved a complete response or very good partial response on induction therapy, the use of maintenance therapy in Spain appears to be low at the time of the study and has not been increased significantly in recent years. The limited use of oral regimens and particularly maintenance therapy in front-line non-SCT patients highlights a key area of MM care in need of improvement to optimize patient care.

Summary points

- Treatment of multiple myeloma has evolved significantly in the past 15 years, with the approval of the first proteasome inhibitor (PI), bortezomib, in 2004, with additional PIs, immunomodulatory agents (IMiDs) and monoclonal antibodies entering the market.
- This retrospective chart review study aimed to describe patient characteristics, treatment patterns and outcomes among newly diagnosed multiple myeloma (NDMM) non-stem cell transplant (non-SCT) patients in a real-world setting in Spain.
- The study included two cohorts of NDMM patients: an 'early cohort' consisting of patients diagnosed between 1 January 2012, and 31 December 2013 and a 'recent cohort' consisting of patients diagnosed between 1 April 2016 and 31 March 2017.
- Among the 113 patients enrolled (early cohort: 65, recent cohort: 48), PI/alkylator-based combinations (48.7%) and PI-based regimens without an alkylator (30.1%) were the most common first-line (1L) therapies.
- Use of PI/IMiD-based regimens increased between the cohorts; PI-based regimens without an alkylator/IMiD decreased.
- Overall use of 1L oral regimens was low (4.4%) but increased between the early cohort (1.5%) and recent cohort (8.3%).
- Fifteen percent of patients received post-induction maintenance therapy in 1L, with regimens being a mix of IMiD-based, PI-based and both IMiD/PI-based.
- Median 1L duration of treatment was 6.9 months and median progression-free survival from start of 1L therapy was 22.5 months.
- The limited use of oral regimens and maintenance therapy in front-line non-SCT patients highlights a key area of MM care in need of improvement to optimize patient care.

Author contributions

Dasha Cherepanov,Dorothy Romanus, Katharina Verleger, and Shelby Corman designed the study. José-Ángel Hernández-Rivas, Mario Arnao, José Maria Arguiñano Pérez, Araceli Rubio, Esther González García, Dunia de Miguel, and Ernesto Pérez Persona collected data. Courtney Johnson and Katharina Verleger analyzed the data. All authors participated in the interpretation of results and the development of the manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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