

Health-related quality of life of multiple myeloma patients after the first-line treatment: results of a prospective cohort study

Qualidade de vida relacionada à saúde de pacientes com mieloma múltiplo após o tratamento de primeira linha: resultados de um estudo de coorte prospectiva

Calidad de vida relacionada con la salud de pacientes con mieloma múltiple después del tratamiento de primera línea: resultados de un estudio de cohorte prospectivo

Received: 08/29/2022 | Reviewed: 09/05/2022 | Accept: 09/08/2022 | Published: 09/17/2022

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Abstract

Objective: The aim of this study was to evaluate whether there was an improvement or a deterioration of health-related quality of life (HRQoL) of multiple myeloma patients (MM), and to assess the associated factors with HRQoL after 12 months of treatment. **Methods:** We performed a prospective cohort study with MM patients in first-line treatment from public and private onco-hematology health services in a Brazilian metropolis. HRQoL, socio-

demographic and clinical variables were obtained by interviews and review of medical charts. HRQoL and peripheral neuropathy (PN) were collected through validated instruments (QLQ-C30, QLQ-MY20, CINCQ). Medians of the HRQoL scores, obtained at baseline and follow-up interviews, were compared. Median HRQoL scores at follow-up were compared by variables. The improvement or deterioration in HRQoL and the association with variables were measured. Results: Thirty-three patients completed the follow-up, with ISS III (25.0 %), on polypharmacy (72.2 %), using a thalidomide+bortezomib-based regimen as first-line (19.4 %), and median age of 66.5 years. HRQoL Summary score, Functioning, Symptom scales, and Future Perspective scores were improved between periods ($p<0.05$). Patients who were on polypharmacy, with severe PN, and with ISS III had deterioration in HRQoL; younger patients had improvement and older patients had deterioration in HRQoL ($p<0.05$). Conclusions: Our study showed that first-line treatment improved HRQoL of patients in the following QLQ-C30 scales: Summary score, Role functioning, Emotional functioning, Fatigue, Pain, and Constipation; and in QLQ-MY20, Future perspective was improved. Our study shows the importance of using patient-reported outcomes during MM treatment.

Keywords: Multiple myeloma; Quality of life; Thalidomide; Bortezomib; Peripheral neuropathy.

Resumo

Objetivo: O objetivo foi avaliar se houve melhora ou piora da qualidade de vida relacionada à saúde (QVRS) de pacientes com mieloma múltiplo (MM) e fatores associados à QVRS após 12 meses de tratamento. **Métodos:** Realizou-se estudo de coorte prospectiva com pacientes com MM em tratamento de primeira linha em serviços de saúde de onco-hematologia públicos e privado no Brasil. QVRS, variáveis sociodemográficas e clínicas foram obtidas por meio de entrevistas e revisão de prontuários. QVRS e neuropatia periférica (NP) foram coletadas por meio de instrumentos validados (QLQ-C30, QLQ-MY20, CINCQ). As medianas dos escores de QVRS, obtidos nas entrevistas basais e de seguimento, foram comparadas. Os escores medianos de QVRS no seguimento foram comparados por variáveis. A melhora ou piora da QVRS e a associação com variáveis foram mensuradas. **Resultados:** Trinta e três pacientes completaram o seguimento, com ISS III (25,0 %), polifarmácia (72,2 %), em uso de talidomida+bortezomibe como primeira linha (19,4 %), e idade mediana de 66,5 anos. O Escore sumarizado, escalas Funcionais e de Sintomas e Perspectiva Futura melhoraram entre os períodos ($p<0,05$). Pacientes em polifarmácia, com NP grave e ISS III apresentaram piora da QVRS; pacientes mais jovens tiveram melhora e pacientes mais velhos pioraram na QVRS ($p<0,05$). **Conclusões:** O tratamento de primeira linha melhorou a QVRS dos pacientes nas seguintes escalas QLQ-C30: escore sumarizado, escala funcional, escala emocional, fadiga, dor e constipação; e no QLQ-MY20, a perspectiva futura melhorou. Nosso estudo mostra a importância de usar resultados relatados pelo paciente durante o tratamento do MM.

Palavras-chave: Mieloma múltiplo; Qualidade de vida; Talidomida; Bortezomibe; Neuropatias periféricas.

Resumen

Objetivo: El objetivo fue evaluar si hubo una mejora o empeoramiento en la calidad de vida relacionada con la salud (CVRS) de pacientes con mieloma múltiple (MM) y factores asociados a la CVRS después de 12 meses de tratamiento. **Métodos:** Se realizó un estudio de cohorte prospectivo con pacientes con MM en tratamiento de primera línea en servicios oncohematológicos de Brasil. Se obtuvieron variables clínicas, sociodemográficas y CVRS a través de entrevistas y revisión de historias médicas. La CVRS y la neuropatía periférica (NP) se recogieron mediante instrumentos validados. Se compararon las puntuaciones medianas de la CVRS obtenidas de las entrevistas iniciales y de seguimiento. Se midió la mejora o empeoramiento de la CVRS y la asociación con variables. **Resultados:** Treinta y tres pacientes completaron el seguimiento, con ISS III (25,0%), polifarmacia (72,2%), usando talidomida+bortezomib como primera línea (19,4%), y una mediana de edad de 66,5 años. La puntuación resumida, las escalas funcionales y de síntomas y la perspectiva futura mejoraron entre períodos ($p<0,05$). Los pacientes en polifarmacia, con NP grave e ISS III presentaron empeoramiento de la CVRS; los pacientes más jóvenes mejoraron y los pacientes mayores empeoraron en CVRS ($p<0,05$). **Conclusiones:** El tratamiento de primera línea mejoró la CVRS de los pacientes en las siguientes escalas QLQ-C30: puntuación resumida, escala funcional y emocional, fatiga, dolor y estreñimiento; y en QLQ-MY20, la perspectiva de futuro ha mejorado. Nuestro estudio muestra la importancia de utilizar los resultados informados por los pacientes durante el tratamiento del MM.

Palabras clave: Mieloma múltiple; Calidad de vida; Talidomida; Bortezomib; Enfermedades del Sistema Nervioso Periférico.

1. Introduction

Multiple myeloma (MM) is an incurable cancer of the monoclonal plasma cells of bone marrow. It accounts for 1 % of all cancers and approximately 10 % of all hematologic malignancies. MM is diagnosed by the presence of clonal plasma cells together with the CRAB criteria: hypercalcemia, renal injury, anemia, and/or bone lesions and the presence of biomarkers of progression (Palumbo & Anderson, 2011; Rajkumar, 2020). MM primarily affects older adults, the median age of patients at

the time of diagnosis is about 65 years (Kyle et al., 2003). In Brazil, patients appear to be diagnosed earlier, with the median age being 60 years (Hungria et al., 2008). The 2019 Global Burden of Disease study showed an age-standardized prevalence of 5.6 cases of MM per 100,000. Changes in life expectancy reflect the global disease burden estimated at 2.5 million Disability-Adjusted Life-Years (DALYs) in 2019, corresponding to the age-standardized rate of 30.26 DALYs per 100,000 inhabitants. Similar prevalence (5.0 cases per 100,000) and higher DALYs (39.5 DALYs per 100,000) were found in Brazil (Institute for Health Metrics and Evaluation (IHME), 2015).

The goals of chemotherapy in MM are to prolong overall survival, to manage symptoms and to reduce or delay organ damage, while preserving quality of life. Survival in MM has improved significantly in the past years, with the introduction of an immunomodulatory drug (IMiD) (thalidomide and derivatives) and proteasome inhibitors (bortezomib and derivatives) (Kumar et al., 2014). Chemotherapy regimens generally containing an IMiD, a proteasome inhibitor or an alkylator, together with a steroid, and even a monoclonal antibody (mAB), followed or not by autologous stem cell transplant (ASCT), are currently used as first-line treatment for newly diagnosed patients (Lu, 2020).

Newer options of drug combinations have been made available for therapeutic regimens (Rajkumar, 2020); however, in Brazil the most common regimens used are based on bortezomib or thalidomide (especially in the public health system) or regimens that combine both (Brasil, 2015; Pessoa de Magalhães Filho et al., 2019). Thalidomide and bortezomib-based regimens are often associated to peripheral neuropathy (PN). This adverse event is treatment-limiting, causes pain, paresthesia, numbness, and tingling, among other symptoms. It can be irreversible if not managed, therefore guidelines recommend clinical assessment of patients during chemotherapy. If PN develops, thalidomide and/or bortezomib doses should be reduced or discontinued. PN is reported to cause deterioration in health-related quality of life (HRQoL) (Kerckhove et al., 2018; Koeppen, 2014; Selvy et al., 2021; Shaheen et al., 2020). Chemotherapy regimens may also influence HRQoL (Roussel et al., 2020; Stewart et al., 2015, 2016).

HRQoL of MM patients becomes an important patient-reported outcome to be evaluated, as well as factors that can influence quality of life outcomes. In spite of treatment improvements, MM still has no cure and patients will live longer with clinical manifestations. Patients will eventually relapse and need subsequent lines of chemotherapy treatment, developing adverse drug events and other disease complications (Ramsenthaler et al., 2016; Warsame & D'Souza, 2019; Zanwar et al., 2019).

Many studies evaluating quality of life of MM patients are cross-sectional studies or clinical trials (Kang & Choi, 2019; Ludwig et al., 2019; Malta et al., 2022; Plesner et al., 2021; Roussel et al., 2020; Stewart et al., 2015); thus, they do not provide information on baseline HRQoL, HRQoL outcomes after chemotherapy treatment, and are not developed in a real-world context. To the best of our knowledge, few longitudinal studies evaluate HRQoL in first-line treatment (Nielsen et al., 2017). Therefore, the aim of this study was to evaluate whether there was an improvement or a deterioration of HRQoL after the first-line chemotherapy treatment of MM patients, and to assess the associated factors to HRQoL achieved after treatment.

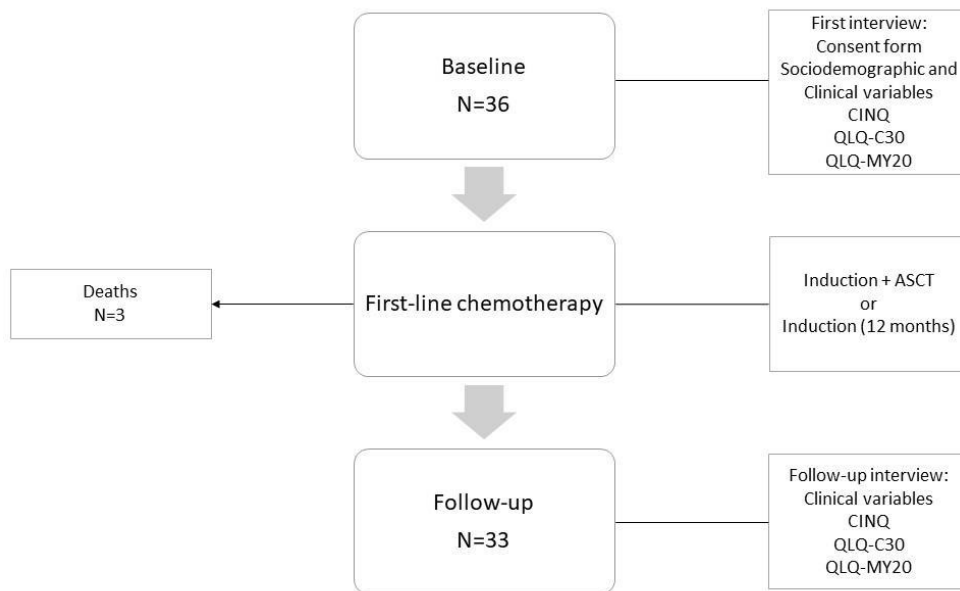
2. Methodology

2.1 Study design and population

We performed a prospective cohort study (Celentano et al., 2019) with newly diagnosed and treatment-naïve MM patients (≥ 18 years-old) attending an outpatient clinic of a public hospital (Hospital das Clínicas, Universidade Federal de Minas Gerais) and a private oncology and hematology clinic (Hematológica clinic, Oncoclínicas group) in Belo Horizonte, Minas Gerais, Brazil. The clinics' databases were assessed, and MM patients were identified through the ICD-10 International Statistical Classification of Diseases and Related Health Problems (code C90 multiple myeloma) and consecutively recruited from April 2019 to February 2020. Patients were met in person before the scheduled medical appointment, when they were

invited to participate and included in the study after signing the consent form. A single face-to-face interview was performed with the participants or their caregivers, using two validated tools to measure PN and HRQoL, along with sociodemographic and clinical questions. Patients were interviewed as soon as they were identified at the clinic, until 30 days after the initiation of chemotherapy, considering patients would be still in the first cycle of chemotherapy (baseline interview). After receiving ASCT, or after about 12 months subsequently starting chemotherapy (patients not eligible for ASCT) patients were interviewed once more (follow-up interview) to assess HRQoL, PN, and clinical data, until first-line chemotherapy would be concluded (Figure 1). Patients' medical records were accessed to complement clinical data within the 12-month follow-up period, through the collection of all medical appointments during the study period.

Figure 1: Patients follow-up.



Source: Authors.

The Research Ethics Committee of the participating institutions approved the study (CAAE n° 05400818.3.0000.5149).

2.2 Variables

The study outcome was the change (improvement or deterioration) of HRQoL achieved at the follow-up interview after initiating the first treatment regimen. HRQoL was obtained through the EORTC QLQ-C30 (Aaronson et al., 1993) and QLQ-MY20 (Cocks et al., 2007) tools. Exposure variables comprised socio-demographic data: sex, age (continuous variable), self-declared skin color, family income, education, public or private health service attendance; and clinical data: ASCT, comorbidities (yes/no), polypharmacy (use of five or more medications), presence of PN symptoms, International Staging System – ISS (based on β 2-microglobulin and albumin parameters to stage the disease at diagnosis) (Greipp et al., 2005), and chemotherapy regimen (thalidomide-based, bortezomib-based, and thalidomide+bortezomib-based regimens). Variables were obtained from a previously tested questionnaire, and clinical data were completed through medical charts review. A validated questionnaire was used to assess PN (Chemotherapy-Induced Neurotoxicity Questionnaire – CINQ) (Leonard et al., 2005)

data.

2.3 Instruments

2.3.1 HRQoL

This study employed the QLQ-C30 tool to assess HRQoL in cancer patients in association with the specific module for MM patients, QLQ-MY20, as recommended. The former is a general tool for cancer patients and the latter is a module to complement the evaluation specific to MM patients. The use of the instruments was authorized by the quality-of-life group of the European Organization for Research and Treatment of Cancer (EORTC), responsible for the elaboration and availability of the instruments, and was exempt from copyright due to the use for the purpose of research. EORTC has translated QLQ-MY20 into Brazilian Portuguese (Etto et al., 2011; Paiva et al., 2014), and our group validated this module in a previous study for Brazilian patients (Malta et al., 2021). It had good validity and reliability characteristics by analysis of content validity, internal consistency, convergent and divergent validity, and temporal reproducibility (Malta et al., 2021).

HRQoL domains from QLQ-C30 (Aaronson et al., 1993) were: Summary score (the sum of C30 scales (Giesinger et al., 2016)), Global health status / QoL, Functional scales (Physical functioning, Role functioning, Emotional functioning, Cognitive functioning, Social functioning), and Symptom scales (Fatigue, Nausea and vomiting, Pain, Dyspnea, Insomnia, Appetite loss, Constipation, Diarrhea, Financial difficulties). Domains from QLQ-MY20 (Cocks et al., 2007) comprised: Functional scales (Future perspective, Body image), and Symptom scales (Disease symptoms, Side effects - adverse effects of treatment). All items have four answer options (1=not at all, 2= a little; 3=quite a bit, and 4=very much), except for the Global health status / QoL domain which contains two items with answers from 0 to 7. Answers were converted to a 0-100 scale to obtain the final score in accordance with the EORTC manual (Fayers et al., 2001).

2.3.2 Peripheral Neuropathy

CINQ is a structured questionnaire containing 29 questions regarding PN symptoms in lower extremities (9 questions), upper extremities (10 questions), and orofacial area (10 questions), the latter not evaluated in the study. It has been translated and validated to Brazilian Portuguese. CINQ's Brazilian version showed good internal consistency, with a Cronbach's alpha of 0.863 (Simão et al., 2014). Initially, patients should answer "yes" or "no" if they have each of the specific symptoms. If the answer was "yes", they would be asked to rate the symptom's frequency through a 5-point scale and the impact of PN symptoms on the individual's ability to perform activities of daily living (ADL) ranging from hardly at all bothered (score 1-3) to extremely bothered (score 4 or 5). We categorized scores 4 or 5 into severe PN, according to the CTCAE v5.0 classification (National Cancer Institute., 2017). We considered the lower extremity and upper extremity areas of major relevance for the occurrence of PN in MM patients.

2.4 Data collection

Interviews were conducted with the help of the Questionnaire Development System (QDS, version 2.6.1.1). Data from medical records were recorded in structured forms developed by the research group. All researchers involved in the data collection were trained and followed up during the first interviews and medical charts collection. A pilot study was carried out in order to standardize the procedures for applying the questionnaires and instruments.

2.5 Statistical analysis

Frequency distribution and measures of central tendency were performed to characterize the population regarding HRQoL and selected exposure variables. The Wilcoxon test was used to compare the medians of the HRQoL scores obtained

at baseline and follow-up interviews.

The median scores at the follow-up interview were analyzed using the Mann-Whitney U test to compare the results for each HRQoL scale by group of binary independent variables. Kruskal Wallis and Bonferroni post hoc tests were used to compare median HRQoL scores between chemotherapy regimens.

To measure the improvement or deterioration in HRQoL we subtracted the follow-up median scores from the baseline median scores domains. The linear regression method was used to measure the association between the score differences and exposure variables in univariate and multivariate analyses. Positive beta values obtained in the final models of Summary score, Global health status / QoL, and Functional scales, from QLQ-C30, and Future Perspective, and Body Image from QLQ-MY20 corresponded to improvement (negative values denote deterioration for these domains) in HRQoL. Positive beta values of Symptom scales from QLQ-C30, Disease symptoms, and Side effects - adverse effects of treatment from QLQ-MY20 corresponded to deterioration in HRQoL (negative values indicate HRQoL improvement).

The effect of age on the outcome was not linear. There was empirical evidence that the difference of score reduces with age. We used a linear and a quadratic term to accommodate this behavior of age. Thus, we calculated the effect of specific age or age groups on the changes in the score differences, considering the mean age of MM patients, and the linear (“Age”) and quadratic terms (“Age²”) obtained from the final models. To find the effect of age on HRQoL after first-line treatment, we used the following formula:

$$\text{HRQoL score difference} = (\text{age} - \text{mean age}) \times \text{linear term} + \text{quadratic term} \times [(\text{age} - \text{mean age})]^2$$

Variables included in the initial model of multivariate analysis consisted of those statistically associated with HRQoL in the univariate analysis ($p < 0.20$) (Bendel & Afifi, 1977). Modeling was performed by applying the stepwise method, initially including all variables followed by sequential deletion to assess the statistical significance of each, and only those with $p < 0.05$ were retained in the final model (backward method).

All statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) version 21.0.

3. Results

3.1 Patients' profile

Thirty-six patients were included in the study, 33 patients completed the follow-up and three patients died during the study period. The median age of patients was of 66.5 years old (min 47, max 87), 52.8 % were females, 41.7 % self-declared white skin color, 61.1 % had low family income (up to three minimum wages= 275 USD), 41.7 % had low education (up to elementary school), and 41.7 % attended the public health service (Table 1).

Table 1: Patients' sociodemographic profile at baseline (n=36).

Variable	n	(%)
Sex		
Male	17	(47.2)
Female	19	(52.8)
Self-declared skin color		
White	15	(41.7)
Not White	21	(58.3)
Household income (1 min. Wage = 275 USD*)		
Low (≤ 3 min. wages)	22	(61.1)
High (> 3 min. wages)	14	(38.9)
Education level		
Low (Never studied + Elementary school)	15	(41.7)
High (High school + Higher education)	21	(58.3)
Type of clinic		
Public	15	(41.7)
Private	21	(58.3)
ISS		
I	7	(19.4)
II	15	(41.7)
III	9	(25.0)
Missing	5	(13.9)
Comorbidities (Yes)	28	(77.8)
Polypharmacy (Yes)	26	(72.2)
ASCT (Yes)	14	(42.4)
Chemotherapy regimen		
Thalidomide-based	15	(41.7)
Bortezomib-based	14	(42.4)
Thalidomide + bortezomib-based	7	(19.4)
Peripheral Neuropathy		
Lower limbs	8	(22.2)
Upper limbs	6	(16.7)

* Date of dollar exchange rate: January 2019. Source: Authors.

Most patients had ISS II (41.7 %), had comorbidities (77.8 %), and were on polypharmacy (72.2 %); 42.4 % had undergone ASCT, and 61.1 % used a thalidomide/thalidomide+bortezomib-based regimen as first-line treatment. Regarding PN, 22.2 % had PN symptoms in lower limbs and 16.7 % in upper limbs.

Three patients died during the study period due to MM complications and did not complete the follow-up. They all had comorbidities, and did not receive ASCT; two attended the public clinic, were on polypharmacy, had no record of ISS and were using a thalidomide-based regimen as first-line treatment. The third was being treated in the private clinic, had ISS III, had a thalidomide+bortezomib-based regimen as first-line of treatment. They were 80, 50, and 54 years old, respectively.

3.2 Changes in HRQoL after the first-line treatment

There were statistically significant ($p < 0.05$) differences for the scores obtained at baseline and follow-up periods for the following scales: Summary score, Role Functioning, Emotional Functioning, Fatigue, Pain, Constipation, and Future Perspective (Table 2).

Table 2: HRQoL scores at baseline and follow-up interviews.

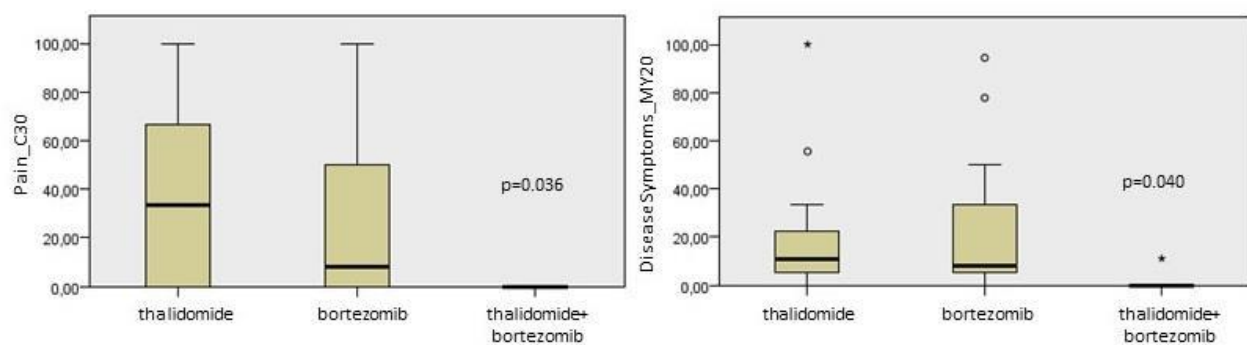
HRQoL scales	Baseline	Follow-up	Wilcoxon test (p-value)
	(n=36)	(n=33)	
	Median		
Summary score	64.53	78.97	0.013
Global health status / QoL	75.00	83.33	0.079
Physical functioning	50.00	60.00	0.236
Role functioning	33.33	100.00	0.006
Emotional functioning	58.33	83.33	0.006
Cognitive functioning	75.00	83.33	0.521
Social functioning	50.00	66.67	0.299
Fatigue	38.89	22.22	0.038
Nausea and vomiting	0.00	0.00	0.899
Pain	75.00	0.00	<0.001
Dyspnea	0.00	0.00	0.757
Insomnia	0.00	0.00	0.349
Appetite loss	0.00	0.00	0.336
Constipation	33.33	0.00	0.018
Diarrhea	0.00	0.00	0.589
Financial difficulties	16.67	0.00	0.547
Future perspective	33.33	66.67	0.009
Body image	50.00	100.00	0.208
Disease symptoms	25.00	11.11	0.065
Side effects – adverse effects of treatment	25.00	20.00	0.180

Source: Authors.

3.3 Comparison of medians of HRQoL scores by variables at the follow-up

The Mann-Whitney test analysis showed that at the follow-up interview (data not shown in Table), patients on polypharmacy had worse scores on the Social Functioning scale ($p=0.047$). Patients who received ASCT had better scores for Cognitive Functioning ($p=0.048$), Insomnia ($p=0.049$), Constipation ($p=0.010$), and also for Summary score ($p=0.049$). Patients with comorbidities had better scores in Global health status / QoL ($p=0.033$) and Role functioning scales ($p=0.040$). Patients with severe PN symptoms in lower extremities had worse scores in the Insomnia scale ($p=0.017$); in upper extremities had worse scores in the Emotional ($p=0.040$) and Cognitive Functioning ($p=0.030$) scales and in the Summary score ($p=0.045$). Kruskal-Wallis and Bonferroni post hoc tests showed that patients on thalidomide + bortezomib-based achieved better scores in the Pain ($p=0.036$) and Disease symptoms ($p=0.040$) scales compared to patients on thalidomide-based regimens (Figure 2). The type of clinic (public or private) showed no statistical difference in any of the HRQoL scales.

Figure 2: Kruskal-Wallis test for HRQoL scores follow-up per chemotherapy regimens.



Source: Authors.

3.4 Mean difference in HRQoL scores from baseline to follow-up

In the univariate analysis (Table 3), we found statistical significance ($p < 0.05$) between HRQoL and sex, type of clinic, having been submitted to ASCT, polypharmacy, PN, skin color, family income, education level, ISS, and age.

Table 3: Association analysis between HRQoL domains and selected variables ($p < 0.20$; $n = 33$).

HRQoL Domain	Score difference between follow-up and baseline															
	Summary score		Global Health Status / QoL		Functional scales		Symptom scales		Future perspective		Body image		Disease symptoms		Side effects	
	β	p	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Female Sex	12.25	0.07	20.09	0.03	10.79	0.10	-14.27	0.09	8.15	0.53	5.56	0.77	-8.83	0.32	-14.67	0.05
Private clinic	-0.19	0.98	-3.14	0.74	-5.34	0.44	-3.13	0.72	10.81	0.42	-40.13	0.03	-3.76	0.68	3.38	0.67
ASCT	-1.27	0.86	-1.94	0.84	-7.11	0.29	0.50	0.95	-17.00	0.19	-20.43	0.29	-0.23	0.98	9.10	0.24
Comorbidities	1.04	0.90	14.83	0.17	10.59	0.17	2.22	0.82	20.78	0.17	18.67	0.40	-10.70	0.30	-12.10	0.17
Polypharmacy	-14.08	0.06	-15.74	0.13	-20.29	0.00	12.25	0.19	10.19	0.49	-21.30	0.32	4.24	0.67	8.15	0.34
PN lower extremities	-8.50	0.28	-24.46	0.02	-10.92	0.16	11.32	0.25	-22.61	0.13	3.33	0.88	18.03	0.08	18.15	0.04
PN upper extremities	-16.33	0.06	-10.34	0.39	-11.16	0.19	16.62	0.12	-2.26	0.89	-58.02	0.01	14.71	0.20	8.83	0.37
White skin	-2.24	0.75	-5.83	0.54	-1.46	0.83	-0.14	0.99	16.29	0.21	-42.22	0.02	-12.90	0.14	-1.63	0.83
High family income	6.34	0.36	5.32	0.58	11.08	0.10	-6.05	0.48	3.76	0.78	23.33	0.23	-8.69	0.34	-15.65	0.04
Low education level	11.51	0.09	10.54	0.27	11.94	0.07	-10.22	0.23	-0.94	0.94	57.05	<0.01	9.40	0.30	-5.50	0.48
ISS_III	-13.52	0.19	-2.83	0.84	-4.05	0.70	15.25	0.22	-44.25	0.01	13.10	0.62	16.37	0.23	6.55	0.58
CR_VTd	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-	1.0	-
CR_thalidomide-based	-3.44	0.73	2.03	0.88	5.81	0.55	7.10	0.56	-15.81	0.40	44.02	0.10	15.24	0.23	1.28	0.91
CR_bortezomib-based	-5.17	0.60	-1.59	0.91	0.68	0.94	5.68	0.64	-7.14	0.70	5.55	0.83	16.40	0.19	6.67	0.54
Age	0.02	0.95	-0.35	0.47	-0.07	0.82	-0.14	0.74	0.47	0.49	0.40	0.68	-0.23	0.61	-0.08	0.83
Age ²	-0.07	0.02	0.01	0.80	-0.07	0.01	0.07	0.04	-0.05	0.40	-0.12	0.17	0.06	0.11	0.06	0.06

CR: chemotherapy regimen; VTd= Thalidomide + bortezomib-based. Source: Authors.

In the multivariate analysis, HRQoL domains were independently associated with comorbidities, polypharmacy, PN, skin color, ISS, and age (Table 4). The most important results are summarized as follows:

- Patients with comorbidities had improvement in Functional scales score difference (+12 units)
- Patients who were on polypharmacy had a deterioration in the Summary score difference and in the Functional scales score difference (-15 units and -19.4 units, respectively).
- PN had a negative impact on HRQoL scales – patients with PN in lower extremities had a deterioration in Global health status / QoL (-24.5 units) and in Side Effects (+18.2); patients with PN in upper extremities had a deterioration in Functional scales (-13.8 units) and Body image (-54 units).
- Patients with low education level had an improvement in Body image score difference (+54.6 units).
- Patients with ISS III had a deterioration in Summary score difference (- 15 units), and in the Body image score difference (-37.8 units) compared with ISS I and II.
- Patients aged from 50 to 70 years-old improved HRQoL regarding summary score, functional scales and symptom scales (summary score: 50 to 60 years: +15 units; 60 to 70 years: +3 functional scales: 50 to 60 years:

+14 units; 60 to 70 years: +2 units; symptom scales: 50 to 60 years: -18 units; 60 to 70 years: -3 units) while patients from older than 70 years had deterioration in HRQoL (summary score: -10 units; functional scales: -9 units; and symptom scales: +12 units).

- Type of clinic, having PN in any body area, family income, education level, and chemotherapy regimen were not associated to any HRQoL domain.

Table 4: Final model between HRQoL domains and independent variables (p<0.05; n=33).

HRQoL domain	Score difference between follow-up and baseline															
	Summary score		Global Health Status / QoL		Functional scales		Symptom scales		Future perspective		Body image		Side effects			
Variable	β	p	β	p	β	p	β	p	β	p	β	p	β	p		
Comorbidities					12.09	0.05										
Polypharmacy	-15.02	0.04			-19.43	<0.01										
PN lower extremities			-24.46	0.02									18.15	0.04		
PN upper extremities					-13.79	0.05					-53.98	0.01				
Low education level											54.56	<0.01				
ISS_III	-15.00	0.04							-37.75	<0.01						
Age	0.01	0.76			0.08	0.75	-0.14	0.74								
Age ²	-0.06	0.03			-0.06	0.02	0.07	0.04								

Source: Authors.

4. Discussion

Our study showed improvement in almost all QLQ C30 and QLQ-MY20 scales after the initiation of the first-line treatment of MM in patients of outpatient clinics. To the best of our knowledge, quality of life in MM was studied only in Brazilian patients eligible to ASCT (Etto et al., 2011). Clinical trials compared HRQoL before and after chemotherapy, showing benefits for specific chemotherapy regimens (Ludwig et al., 2019; Plesner et al., 2021; Roussel et al., 2020). Our investigation is a longitudinal study conducted in public and private outpatient clinics and analyzed the first-line treatment used in care of MM patients in a Brazilian metropolis. The findings are in line with a systematic review presented that included eleven longitudinal studies and reported that first-line patients had large and medium HRQoL improvements in global quality of life, physical functioning, fatigue, and pain scales (Nielsen et al., 2017)

Patients using thalidomide + bortezomib-based regimens had better scores than thalidomide-based regimens in the Pain and Disease Symptoms scales at the follow-up. However, there was no significant difference between the regimens regarding improvement or deterioration of HRQoL in the multivariate analysis. Perhaps we found no statistical differences in the improvement/deterioration due to the homogeneity of regimens available in our sample. Similar results were observed in a cross-sectional analysis (Malta et al., 2022), where median scores were similar between therapeutic regimens; but the Global health status / QoL scale was different for patients in remission compared to patients in treatment, and Body image was slightly different for patients using VTd compared to patients in remission.

PN leads to deterioration of HRQoL (Mols et al., 2014), and it is also associated to chemotherapy regimens based on thalidomide and bortezomib (Kerckhove et al., 2018). In our study, severe PN in different body areas reflected worse HRQoL in almost all domains. This result is in accordance with another study which also found worse scores on almost all QLQ-C30

sub scales for MM patients with PN, and higher grades of PN reflected in worse scores on QLQ-CIPN20 subscales (Beijers et al., 2016). In another analysis, our group found that MM patients using thalidomide and bortezomib-based treatment showed a high frequency of PN, which affected ADL and led to worse HRQoL. Thus, regardless of the chemotherapy regimen used, patients should be monitored for adverse events from the beginning of the first-line treatment.

The results found for patients with comorbidities were unexpected, as they achieved better HRQoL scores in all the analysis performed. In a systematic review, the authors found an inverse relationship between the number of medical conditions and the quality of life relating to physical domains in all studies. They address this finding to the presence of confounders, such as age, which was controlled in our analysis (Fortin et al., 2004). Of note, we did not assess the number of comorbidities neither the severity of each condition, which could explain the results found. In contrast, having polypharmacy reflected deterioration of the Summary score and Functional HRQoL scales, and also lowest median on the functional scale at follow up. Polypharmacy has already been shown to deteriorate quality of life in life-limiting illness (Schenker et al., 2019) and elderly patients (Tegegn et al., 2019), as well as diminished HRQoL in MM patients (Malta et al., 2022). Nonetheless, not all patients with comorbidities in our study were on polypharmacy at follow-up, according to the medical records.

Patients aged >65 years have been found to score better on emotional functioning ($p<0.05$) and financial problems ($p<0.01$) compared with patients ≤ 65 years. In addition, patients aged ≤ 65 years reported better body image and future perspective ($p<0.01$) whereas younger patients had worse HRQoL compared to the normative population (without MM) than elderly (van der Poel et al., 2015). In our study, changes in HRQoL behaved differently according to the age of patients, considering its non-linear effect on the score differences. We found improvement in summary scores, functional scales, and symptom scale among patients aged from 50 to 70 years; however, younger age strata (<60 years) showed better quality of life outcomes (higher scores). In contrast, older patients (>80 years) had deterioration in HRQoL. Older patients have fewer options of chemotherapy regimens and are often ineligible to ASCT, which reflects on a worse prognosis (Zanwar et al., 2019)

Some studies have evaluated the so called minimally important differences (MID) to establish the clinical meaning of HRQoL changes among patients with MM (Sully et al., 2019). We did not perform the MID estimation in our study, focusing on the statistical significance of changes in HRQoL, which might not represent a clinically relevant improvement or deterioration. In addition to this, we recognize other limitations of our study such as the small sample size of the cohort, the short time interval between ASCT and follow-up and missing data regarding relevant clinical variables, such as ISS and performance status (which was unavailable in most medical records). We emphasize that MM is a rare disease (low incidence); additionally, our recruitment phase had to be interrupted due to the Covid-19 pandemic, which limited the enrollment of newly diagnosed patients. Therefore, we acknowledge our results must be interpreted with caution. Still, we highlight strong points of our study, such as including patients with different profiles from private and public health clinics from a Brazilian metropolis, the follow-up of first-line patients since diagnosis, considering the low incidence of the disease, and being able to assess HRQoL in two different moments, reinforcing the importance of chemotherapy treatment in MM.

5. Conclusion

Our study showed that first-line treatment improved HRQoL of MM patients in the following QLQ-C30 scales: Summary score, Role functioning, Emotional functioning, Fatigue, Pain, and Constipation; in QLQ-MY20, Future perspective was improved after chemotherapy. However, patients who presented severe PN symptoms in any body area had deteriorated HRQoL. Therefore, our study results emphasize the importance of using patient-reported outcomes during MM patients' treatment to monitor both HRQoL and adverse events.

Our study should be continued, with a longer follow-up period and more patients recruited. Newer chemotherapy options are becoming available in Brazil and thus further real-world studies are needed.

Acknowledgments

We thank the collection sites, Hospital das Clínicas / UFMG, Hospital Alberto Cavalcante / FHEMIG, and the Hematológica clinic / Grupo Oncoclínicas, for the partnership and support in the collection of research data.

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