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ORIGINAL RESEARCH

Evaluating Treatment Outcomes on Health-Related Quality of Life in Multiple Myeloma Patients

Ashok Kumar[1], Rahul Kumar[2], Mithu Bhowmick[3], Sweety Kumari[4]

[1,2,3]Department of Internal Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India
[4]Department of Internal Medicine, AIIMS Rishikesh, India

Corresponding author
Rahul Kumar
Department of Internal Medicine, Vardhman Mahavir Medical College & Safdarjung Hospital, New Delhi, India
Email: rahuligims@gmail.com

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ABSTRACT

Background: Advances in multiple myeloma (MM) treatment enhance survival; however, they may impair QOL.The present study aimed to evaluate treatment-related Health-Related Quality of Life (HRQoL) scores among patients undergoing treatment with novel agents. **Methods:** This six-month prospective study was conducted among adult patients with ≥18 years who newly diagnosed with MM (NDMM)of either sex. Demographic, co-morbidities, laboratory investigations, and distribution of Bense-Jones protein were recorded at baseline. Study outcomes were recorded as a response to self-reported European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30 version 3.0) at baseline, 4thand 6thmonth follow-up. **Results:** Total 31 patients were included withmean age of 60.29 years. Hypertension was the most common comorbidity observed in 48.39% of patients, followed by chronic obstructive pulmonary disease in 16.13%. Significant ($p<0.001$) improvement was observed in mean global health statusfrom baseline (48.66) to 6th months (63.39).Additionally, mean functional scales including physical (40.65 vs. 58.10), role (46.77 vs. 66.67), emotional (61.02 vs. 77.78), and social (48.39 vs. 59.52) along with mean symptom scales including fatigue (51.61 vs. 39.70), pain (59.14 vs. 39.51), and dyspnea (41.93 vs. 21.43), were significantly improved from baseline to 6th month with $p<0.001$ after receiving treatment. Overall summary score of both the scales showed significant improvement from baseline to 4th and 6th months with $p<0.001$. **Conclusion**: The mean score of HRQoL significantly improved with the treatment of MMmaking it an important measure of QoL among patients with MM.

Keywords: Hematological malignancy, QoL, EORTC, functional scales, global health status, symptom scales

INTRODUCTION

Multiple myeloma (MM) is a blood cancer resulting fromthe abnormal growth of plasma cells in the bone marrow and is linked to the detection of monoclonal protein in blood and/or urine.[1,2]The age-standardized rate of MM incidence was 1.78 per1,00,000 people, with a mortality rate of 1.14 per 1,00,000 people globally,while it contributes to 1.19% of all cancers in India with an incidence rate of 1.36% in men and 0.99% in women.[3,4]The MM is associated with complications such as renal insufficiency, anemia, abnormal bone radiographs, and hypercalcemia,[2] which leads to increased mobility and mortality among patients with MM. Hence, proper management of these complications is important for the patient's overall quality of life (QoL) and survival.[5]

Recently, advances in MM treatment like autologous stem cell transplantation, alkylating agents, corticosteroids, proteasome inhibitors, immune modulators, and monoclonal antibodies have improved patient survival.[6]However, with the improvement in survival, more concern is arising about treatment-related side effects. The high burden of MM-related symptoms,treatment-related toxicities, and psychosocial effects adversely impact the health-related quality of life (HRQoL).Clinicians in developing nations such as India confront the combined issue of facilitating access to innovative pharmacological agents while also increasingthe QoLofpatients with MM through better supporting measures.

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The HRQoL is now considered as an important criterionto evaluate the effectiveness of treatments and therapies and is gaining considerable attention.[7]Generally, HRQoL is performed based on the self-reported questionnaire. The European Organization forResearch and Treatment of Cancer (EORTC)questionnaire is a commonly used tool for assessment of HRQoL in patients with MM.[8,9] Although previous literature comprehensive insights intothe QoL of patients with MM, they have predominantly focused on Western populations.[10]To the best of our knowledge, few studies of HRQoL in Indian patients with MM have been conducted.[11-13]However, existing HRQoL data cannot be used to compare the QoL across MM treatments due to variations in study populations, treatments, the absence of comparative trials, and differing methodologiesusedin HRQoL analysis.[14]Thus, the present longitudinal study aimed to gain in-depth knowledge about HRQoL in patientswith MM. This studywill help in the management of MM patientsby better understanding the extent to which MM treatment impacts HRQoL.

MATERIALS AND METHODS

This prospective, longitudinal, observational study was conducted over durationof 18 months from 2018-20.Patientsof either sex, aged≥18 years,newly diagnosed withMM (NDMM)based on clinical assessment, and laboratoryfindings and who hadnot received chemotherapy were included in the study. Patientswith MM who were onchemotherapy, and who were dropped out or died before completion of the study were excluded. Written and informed consent was taken from all the patients prior to study enrollment. The present study was ethically approved by ethical committee and was in accordance with the principles of declaration of Helsinki.

The included patients received novel agents such as combination of dexamethasone, lenalidomide, and bortezomib. Treatment prophylaxis of herpes zoster was given in bortezomib receiving patients.

Demographic, co-morbidities,laboratory investigations, and distribution of Bense-Jones protein were recorded at baseline. Included patientswere assessed based on a self-reported questionnaire of European Organization for Research and Treatment of Cancer quality of life questionnaire (EORTC QLQ-C30 version 3.0) at baseline, 4th,and 6thmonth follow-up.

The EORTC-based questionnaire is a comprehensive tool for evaluating the QoL of cancer patients in clinical trials. It encompassesthe QLQ-C30, which is divided into six functional domains (physical, role, emotional, cognitive, and social) and nine symptom domains (fatigue, nausea and vomiting, pain, dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) in addition toglobal health status/ QoL. Most items are related on a four-point Likert scale ranging from ‘not at all' to ‘very much', except items 29 and 30 of QLQ-C30, which use seven-point Likert scale from ‘very poor' to ‘excellent'. Scores are scaled from 0 to 100; higher scores indicate better functioning in functional domains and greater symptom severity in symptom domains.[15] Recruited patients were followed up for sixmonths.

Outcomes were recorded as aself-reported responsetoEORTC questionnaire.A change in score of 6 points or more is considered a clinically meaningful difference.

Statistical analysis

Statistical analysis was performed using IBM Statistical Package of Social Sciences (SPSS) version 21.0. Qualitative data represented as number and percentage while quantitative data expressed as mean (standard deviation [SD]) and compared using paired t-test at baseline and interim follow-ups of 4th and 6th month. Descriptive statistics was applied to describe the population and individual component of EORTC questionnaire.A p-value of <0.05 was considered as statistically significant.

RESULTS

Baseline characteristics

Demographic and baseline disease characteristics of 31 patients were described in table 1.Out of 31, two patientswere died and one participant was lost to follow-up before completing 6th month follow-up questionnaire. The mean age of study patients was 60.29 years and majority (38.71%) of patients aged between 61-70 years, followed by 51-60 years (32.26%), 41-50 years(16.13%), and 71-80 years (12.90%). The study included 58.06% of men patients and 41.94% of women patients.Hypertension was the most common co-morbidity observed in 48.39% of patients, followed by chronic obstructive pulmonary disease (COPD) and type 2 diabetes mellitus (T2DM) observed in 16.13% and 9.68% patients respectively.The mean hemoglobin and serum albumin-globulin ratio was 8.45g/dL and 0.53, respectively. Total 67.74% of patients had hemoglobin of <10 g/dL.The mean serum calcium was 11.06 mg/dL with 48.4% patients had hypercalcemia (serum calcium level >11 mg/dL).The mean serum creatinine was 4.70 mg/dL with 74.2% of patients had serum creatinine levels of >1.2 mg/dL and 61.29% of patients had serum creatinine level of >2 mg/dL (Figure 1a and 1b).

Assessment of responses to EORTC questionnaire

Statistically significant improvement ($p<0.01$) wasobserved in mean score of global health status/ QoLfrom baselineto the 4th and 6th month follow-up (48.66, 54.30, and 63.39 respectively) after receiving treatment(Table 2).There was significant improvement in themean score of functional scalesincluding physical (40.65vs. 58.10; $p<0.001$), role (46.77 vs. 66.67; $p<0.001$), emotional (61.02 vs.

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77.38; p<0.001),and social (48.39 vs 59.52; p<0.001) from baseline to6th month follow-up.Additionally, there was a significant improvement in the mean score of symptom scales including fatigue (51.61 vs. 39.70; p<0.001), nausea and vomiting (22.58 vs. 12.50; p<0.015), pain (59.14 vs. 39.51; p<0.001), dyspnea (41.93vs. 21.43; p<0.001), insomnia (38.71 vs. 22.62; p<0.002), appetite loss (27.96 vs. 17.86; p<0.015), and diarrhea (8.60 vs.2.38; p<0.048) from baseline to 6th month. Other functional and symptom scales were comparable at corresponding time points. Overall summary score of both the scales showed significant improvement from baseline to 4th and 6th months with p<0.001.

Table 1: Demographic and baseline disease characteristics

Parameters	Number of patients (N=31)
Age [years], mean (SD)	60.29 (9.15)
Age group [years]	
41-50	5 (16.13)
51-60	10 (32.26)
61-70	12 (38.71)
71-80	4 (12.90)
Sex	
Men	18 (58.06)
Women	13 (41.94)
Comorbidities	
Hypertension	15 (48.39)
COPD	5 (16.13)
T2DM	3 (9.68)
CAD	2 (6.45)
CVA	2 (6.45)
DCMP	2 (6.45)
CHF	1 (3.23)
Hypothyroidism	1 (3.23)
Laboratory investigations, mean (SD)	
Hemoglobin (g/dL)	8.45 (2.36)
ESR (mm/h)	100.42 (45.53)
Serum albumin (g/dL)	3.07 (0.64)
Serum albumin and globulin ratio	0.53 (0.19)
Serum calcium (mg/dL)	11.06 (1.31)
Serum creatinine (mg/dL)	4.70 (4.06)
Bense-Jones protein	5 (16.13)
Data presented as n(%), unless otherwise specified. CAD, coronary artery disease; CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DCMP, dilated cardiomyopathy; T2DM, type 2 diabetes mellitus; ESR, erythrocyte sedimentation rate.	

Table 2: European Organization for Research and Treatment of Cancer quality of life questionnaire outcome

Scale	Baseline	After 4 months	After 6 months	p-value
Global health status/ QoL	48.66 (13.45)	54.30 (15.20)	63.39 (11.42)	<0.001[a] <0.001[b]
Functional scales				
Physical functioning	40.65(16.63)	49.03 (16.65)	58.10 (16.71)	<0.001[a] <0.001[b]
Role functioning	46.77 (22.94)	55.91 (16.97)	66.67 (15.04)	<0.001[a] <0.001[b]
Emotional functioning	61.02 (16.30)	70.97 (14.89)	77.38 (13.77)	<0.001[a] <0.001[b]
Cognitive functioning	62.90 (20.05)	64.52 (15.36)	69.64 (15.75)	0.238[a] 0.094[b]
Social functioning	48.39 (19.89)	55.38 (14.52)	59.52 (13.17)	0.001[a]

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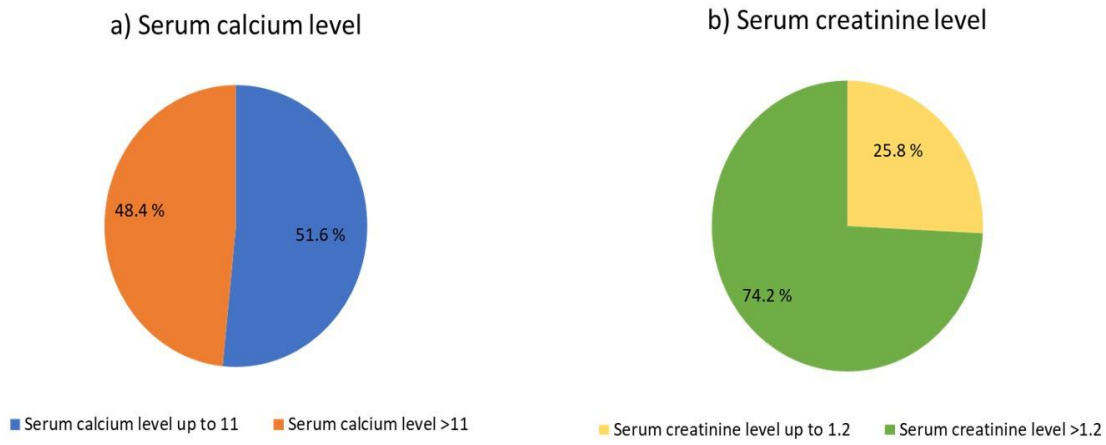
				<0.001[b]
Symptom scales				
Fatigue	51.61 (18.26)	44.46 (15.70)	39.70 (14.95)	<0.001[a] <0.001[b]
Nausea and vomiting	22.58 (19.03)	19.89 (18.96)	12.50 (15.47)	0.163 [a] 0.015 [b]
Pain	59.14 (20.57)	48.39 (16.86)	39.51 (14.73)	<0.001[a] <0.001[b]
Dyspnea	41.93 (29.78)	30.11 (24.88)	21.43 (18.62)	<0.001[a] <0.001[b]
Insomnia	38.71 (22.93)	32.26 (21.92)	22.62 (20.39)	0.042 [a] 0.002 [b]
Appetite loss	27.96 (25.96)	19.35 (20.68)	17.86 (16.93)	0.029 [a] 0.015 [b]
Constipation	30.11 (27.70)	27.96 (21.25)	17.86 (19.21)	0.331 [a] 0.054 [b]
Diarrhea	8.60 (14.83)	3.23 (10.02)	2.38 (8.74)	0.067 [a] 0.048 [b]
Financial difficulties	54.84 (30.49)	58.07 (25.77)	47.62 (23.0)	0.163 [a] 0.208 [b]
Summary score	59.93 (12.57)	66.94 (10.50)	72.58 (8.17)	<0.001[a] <0.001[b]

Data presented as mean (SD).
QoL, quality of life
*[a], p-value, baseline vs 4 months, *[b],p-value, baseline vs 6 months

Figure 1: Distribution of a) serum calcium and, b) serum creatinine level



DISCUSSION

The present longitudinal, observational study assessed the HRQoL in patients of NDMM.The key findings from the study are i) The incidence of MM was common in older age patients; ii) Higher predominance of men; iii) Majority of patients with MM had high serum calcium and creatinine levels; iv) There was statistically significant improvement in mean global health status, functional, symptom scales, and overall symptom score.

Demographic characteristics suggest that the majority of patients were aged between 60-70 years, with mean age of 60.29 years. The results were consistent with previous studies.[16,17] The average age of 64 and 59 years was reported by Fausad et al. and Mathew et al. respectively in Indian population.[16,17]Similarly, in the present study the men-to-women ratio was1.4, consistent with the various studies conducted across India and globally, showing male preponderance among patients with MM.[4,17-20]

Clinical profile of MM was assessed in terms of co-morbidities and lab investigations at baseline. Co-morbidities increase the risk of death in MM patients and affect both progression free and overall survival. Moreover, comorbidity indirectly affects the prognosis by altering the choice of treatment. In the present study, hypertension was the most common co-morbidity among majority of participants followed by COPD,and T2DM. Ramani et al., also reported hypertension and COPD as most common co-morbidities along with T2DM among Indian patients with MM.[1]Therefore,rather than considering solely

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relying on specific age cut-offs,assessing co-morbidities aids in better understanding of status of patients with MM, and maximum tolerability to various treatment options.[21]

The average hemoglobin was 8.45 mg/dL and 67.74% ofpatients had myeloma associated anemia (Hb <10 g/dL). Thesefindings align with previous studies which reported anemia in 72%,[19] 50%,[17] and 60.7%[18] of patients from Indian and Asian population. However, Kaur P. et al., reported a higher incidence of MM associated anemia in 92.8% of patients.[22] The variation in these findings could be attributed to difference in the number of patients enrolled in respective study group. Therefore, individuals with MM exhibit an association with anemia.

Serum albumin is considered as an important prognostic factor in MM. Kim, J. et. al., found that there is an association between low serum albumin levels and severity of MM.[23] Present study reported a mean albumin of 3.07 mg/dL and results were comparable with reported literature (3.0 -3.05 g/dL).[17,23]

Hypercalcemia being an important diagnostic criterion in MM,48.40% of patients reported hypercalcemia and results were comparable with the previous studies.[18,22] It is the most common metabolic complication of MM andstrict guidelines regarding its treatment is essential in patients with MM.[24]Around 61% of patients reported renal impairment (serum creatinine level >2 mg/dL) in present study andthese results were consistent with the previous studies thatreported renal impairment in more than 50% study participants.[22,25] Therefore, the above mentioned results along with the present study reveal that hypercalcemia and increases creatinine levelsare underlying cause of renal impairment among patients with MM, characterized by precipitation of monoclonal and light chain antibodies in collecting and distal tubules.[25]

In a recent global study including 15,386 individuals from various backgrounds, normative HRQoL data was derived using the EORTC QLQ-C30 questionnaire. The study revealed that the mean GHS/QoL score was 66.1.[26]This score is slightly higher than those observed in patients with MM in thepresent study (63.39vs. 66.1). Previously reported literature from Denmark (mean score 61.0)[27] and Greece (mean score 62.60) have also reported similar results.[28]However other studies from India and France have shown comparatively lower QoL scores (55.30 and 57.80, respectively).[11,29] These differences in scoresmay bedueto enrolment of patients at different phases of treatment. The findings indicate that patients with MM experienced notably lower levels of QoL.

With regards to functional domains, in present cohort, treatment with novel agents showed a trend towards improvement over a period of six-months. Additionally, an introduction of novel treatment agents has notably enhanced the prognosis and extended the overall survival of patients diagnosed with MM.[30]The present study showed overall improvement in HRQoL owing to global status of QoL, functional and symptom scales and the results were consistent with the previous studies.[16,31]A short survey study by Etto et al, has highlighted the beneficial impact of ASCT on the QoL for Brazilian MM patients.[32] Similar result was observed in real world study wherein 118 patients who underwent ASCT showed significant enhancement in overall HRQOL post-ASCT suggesting a positive influence on the overall management of the disease.[33]However, some studies indicate a temporary negative effect on HRQOL following the utilization of novel agents.[34]

Martin et al., in their study found significant improvement in physical and role functioning score in addition to symptom score from baseline.[35,36]A noteworthy Dutch study with a sample size of nearly 2000 people shown that the variations in physical role and cognitive functioning, global QOL , exhaustion, discomfort, and dyspnea were clinically meaningful.[37]On parallel lines, previously published randomized phase III trial with NDMM patientsshowed that treatment with both lenalidomide and low-dose dexamethasone improved HRQoL of patients with MM from baseline to 18 months across all pre-selected domainsof Core Quality of Life questionnaire and EuroQol 5 Dimension (QLQ-C30 and EQ-5D).[38]Roussel M. et al. also showed similar results in 792 patients with NDMM where addition of carfilzomib to a combined treatment of lenalidomide, and dexamethasone resulted in significant improvement in HRQoLin terms of physical functioning, and role functioning scores.[35]A retrospective study from India consisting 453 patients reportedsignificant improvement in the scores of QoL in patients with NDMM.The study concluded that simple and patient reported scoring system for symptom scale and overall perceived QoL is an important criterion to predict survival outcomes in NDMM patients.[39]Although, most of the studies reported overall improvement in QoL in NDMM patients, contradictory results were also obtained in several studies.[34,40,41]Most patients either improved using the novel agents suggesting that treatment does not impair patient's physical performance status or potential frailty.

Results of the present study and analysis of overall literature suggests that assessment of HRQoL in patients with MM is an important criterion and should include as an QoL outcome in MM related clinical studies.

Limitations

The study had severallimitations. Firstly, it is a single centre study with small sample size with limited follow-up period.The study only consider results from the single centre hence correlation with overall population is restricted. A recently published study from Indian literature examined factors influencing

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Health-Related Quality of Life (HRQoL) in patients receiving inpatient and outpatient care with novel agents. The study identified several factors linked to poorer HRQoL, including older age, lower educational attainment, chemotherapy, palliative care, surgery, advanced cancer stage, and disease progression.[13] However, it's important to note that the present study does not establish such correlations due to missing data pertaining to socioeconomic status and cancer stages. Therefore, further long-term investigation is warranted to elucidate these associations across diverse population.

CONCLUSION

Advancement in treatment options in MM resulted in increased overall survival. The results from the present study confirmed the improvement in HRQoL in patients with MM during treatment. Assessment of HRQoL score provides a valuable addition to the conventional endpoints in clinical studies related to MM, enabling a consideration of patients' perspectives.

Statements and Declarations

Competing Interests: None
Conflict of Interest: None

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