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Geriatric Assessment and Quality of Life Changes in Older Adults with Newly Diagnosed Multiple Myeloma Undergoing Treatment

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Abstract

Objective: Multiple myeloma (MM) is a cancer of older adults with a median age at diagnosis of 70 years. Our study aimed to understand the changes that occurred in geriatric domains and quality of life parameters as older adults underwent treatment for MM over 6-months following initial diagnosis.

Methods: This was a secondary analysis of a prospective cohort study of 40 adults aged ≥65 with newly-diagnosed MM who completed the Cancer and Aging Research Group geriatric assessment and the Functional Assessment of Cancer Therapy (General and subscale Gynecologic Oncology Group-Neurotoxicity) quality of life tool at baseline and at 6 months following treatment initiation.

Results: Thirty-six participants completed 6-months of follow-up. There was no significant change in geriatric domains, including dependence in instrumental activities of daily living (IADLs). Compared to baseline, mental health improved at 6-months of follow-up (Mental Health

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Inventory-17 score, median 77.1 versus 84.3 at baseline and 6-months respectively, p<0.001). Objective physical performance as measured by the Timed Up and Go test showed a trend towards improvement (12.3 versus 11.0 seconds, p=0.057) and remained stable or improved in almost all (30/32, 93.8%) of the adults using the minimum clinically important difference threshold.

Conclusion: From baseline to 6-months of follow-up, older adults with MM showed improvement in mental health but otherwise remained stable with regards to function and overall quality of life. Timed Up and Go Test may provide a dynamic indicator of functional status and needs to be further evaluated in future studies.

Keywords

Multiple Myeloma; Autologous stem cell transplant; older patients

1.0 Introduction

Multiple myeloma (MM) is a neoplasm characterized by the clonal proliferation of malignant plasma cells within the bone marrow associated with major morbidity and mortality [1]. It accounts for approximately 10% of all hematologic malignancies. In Western countries, the median age at diagnosis is 70, making MM a disease that primarily burdens older adults [2]. As an incurable malignancy, the goals of MM treatment include durable disease control in order to ensure both prolongation of a patient's survival and preservation of functional status and quality of life (QoL).

Frailty is often operationalized as a state of physiological vulnerability to stressors that results from age-related decline in biological systems and manifests clinically as greater risk of adverse outcomes[3]. Currently, there are a number of geriatric tools and frailty assessments for adults with MM for prognostication of progression-free survival, overall survival, treatment-related toxicity and health care utilization rates[4–8]. However, all of these tools historically have only been applied at pre-therapy baseline. A longitudinal geriatric assessment could provide additional value in oncology, as domains tested in these assessments may dynamically change over time, as a result of competing factors of disease and remission status, chemotherapy toxicity and the development of new comorbidities unrelated to myeloma [9]. The longitudinal assessment of frailty as it changes over time in adults with MM undergoing treatment is largely unexplored.

Additionally, the impact of both the disease and treatment on patient's QoL trajectory is imperative to understand. Previous studies have shown that older adults with cancer often value independence, QoL, and symptom management more than traditional clinical trial response criteria, such as overall response rates, progression-free or overall survival[10]. While QoL is increasingly being measured as an outcome in clinical trials, there is a paucity of data in this area in 'real-world' patients and especially longitudinally in older adults with cancer undergoing treatment.

In order to fulfill previous knowledge gaps in this area, we conducted a secondary analysis of data from a previously conducted prospective study to understand short-term changes over six months in various geriatric domains and QoL in older adults with newly-diagnosed

MM initiating treatment. We hypothesized that the receipt of treatment in these patients would not lead to a significant decline or deterioration in both measured geriatric domains as well as overall QoL.

2.0 Methods

2.1 Patient Population and Study Design

This study is a secondary analysis of a pilot prospective cohort study of older adults with newly-diagnosed MM, which aimed to estimate the prevalence of impairments in specific geriatric domains [11]. Study participants were recruited from two academic cancer centers Siteman Cancer Center, St. Louis, MO and Duke Cancer Institute between 2012–2015. Any patients with newly diagnosed MM and age ≥ 65 years were eligible, with the exception of patients with life expectancy < 6 months or concomitant amyloidosis. Geriatric assessments and QoL was measured at both baseline (within 3-months of diagnosis) and 6-months following initial assessment (+/−1 month). At the time of the baseline assessment, 17 individuals were treatment naïve and 23 had initiated treatment with further details provided in the original analysis. The only geriatric domain that is known to differ between patients who had versus had not started myeloma therapy at the time of the baseline assessment was greater number of medications among patients who had started therapy [11]. This study was approved by the institutional review board at both institutions. All patients were registered through the Siteman Cancer Center database at Washington University and gave written informed consent.

2.1 Myeloma Assessment

Disease parameters recorded at baseline included: stage using the International Staging System(ISS)[12], fluorescent *in situ* hybridization (FISH) / cytogenetic abnormalities, and treatment course (autologous stem cell transplant [SCT] versus a non-transplant-based approach [non-SCT]). The overall response rate (during the 6-month assessment period) and survival from baseline was also documented.

2.2 Geriatric Assessment

Geriatric assessment was conducted using the Cancer and Aging Research Group Geriatric Assessment Tool (CARG)[13]. This assessment included previously validated measures of functional status and psychological state [14] and cognition[15]. Physical performance was measured using the Timed Up and Go Test [16]. The minimum clinically important difference for the Timed Up and Go Test (TUG) has been previously defined as 3.4 seconds[17]. Consequently, patients were categorized as improved if the TUG changed by a minimum of 3.4 seconds or if they were unable to complete the test at baseline but could complete it at follow up.

2.3 Quality of Life

The Functional Assessment of Cancer Therapy - General (FACT-G)[18] and the Gynecologic Oncology Group-Neurotoxicity subscale (Ntx)[19] was used to assess global quality of life and symptoms. A neurotoxicity scale was specifically examined to assess for neuropathy which is a known side effect of myeloma chemotherapy regimens [20, 21]. Both

of these instruments have been validated with higher scores indicating better overall QoL[19, 22]. Minimally important differences (MID) ranges have been defined (3–7 for FACT-G [23] and 2–3 for Ntx subscale[24]) in the literature. For our analysis, we used the median provided in each range with 5 and 2.5 changes in scores as being the MID for FACT-G total and Ntx subscale respectively.

2.4 Statistical Analysis

Summary statistics, including the mean, standard deviation, proportion and frequency, were used to describe the patient characteristics and outcomes. Geriatric assessments and QoL scores were summarized at baseline and at the 6-month time point separately, as well as the absolute change from baseline to 6-months. Changes in geriatric domains across all patients from baseline to 6-months were tested using the McNemar test or the Wilcoxon signed rank test for categorical and continuous variables respectively. The Wilcoxon rank sum test and chi-square test were used to compare continuous and categorical outcomes between patients who underwent SCT versus those who did not. The Wilcoxon rank sum test was also used to compare the psychological status (Mental Health Inventory-17 total score) between patients who were stable versus those that showed an improvement in their objective physical performance measure using MID as defined above for the Timed Up and Go Test. Statistical significance was defined at the α=0.05 level of significance and all tests were two-sided. No multiple testing adjustment was performed, however, all test results are considered hypothesis generating. Overall survival was estimated from the time of study enrollment until death due to any cause, using the Kaplan-Meier method. All analysis was done using SAS version 9.4.

3.0 Results

At baseline, 40 patients were enrolled in the study and 36 patients completed the 6-month follow-up (3 patients died prior to the 6-month assessment and 1 patient did not return to clinic). Baseline demographic and disease characteristics of the 36 patients who completed the 6-month follow up are outlined in Table I. The median age was 70 years and 24/36 (66.6%) were males. Sixteen patients underwent a SCT prior to the follow up assessment with a median time from initial assessment to SCT being 82 days (range 17–198 days). Four individuals out of the 36 had a follow-up phone interview and therefore measures requiring physical assessment such as the TUG test could only be assessed on 32 patients.

3.1 Geriatric Assessment Changes

Overall changes in the measured geriatric domains over the period of 6-months are outlined in Table II. There was no statistically significant change in patient's body mass index or Karnofsky performance status. Polypharmacy was prevalent both at baseline and at 6-months, with older adults with MM taking a median of nine medications. Functional and activity status as measured by the number of dependence in instrumental activities of daily living (IADL) domains, number of falls, and the Medical Outcomes Study (patients limited in moderate activity) remained stable over the 6-month interval. Cognitive status using the Blessed Orientation-Memory-Concentration (BOMC) test showed that most individuals' scores were within normal limits and this did not statistically change over a period of 6-

months. Patient's psychological status measured using the Mental Health Inventory-17 total score improved over the period (77.1 at baseline versus 84.3 at 6-months, p-value <0.001). There were no significant differences in the geriatric domains noted over the 6-month interval in patients that had undergone a SCT versus not apart from body mass index which significantly declined in the SCT cohort (Appendix Table IA).

Physical performance, assessed with the TUG test, showed a trend toward improvement as patients underwent treatment (12.3 seconds at baseline versus 11.0 seconds at the 6-month follow-up, p=0.057, Table II). There were no significant differences noted between the SCT versus the non-SCT group (Appendix Table IA). At the 6-month follow up, information on TUG was present for a total of 32 patients. Using the minimum clinically important difference for TUG test 30/32 (93.8%) of the patients remained stable or improved [stable (20/32, 62.5%) and improved (10/32, 31.3%)] in their objective physical functioning following 6-months of treatment. Among patients with improved versus stable physical functioning as defined by the MID for TUG, there was no difference noted in their psychological status using the Mental Health Inventory-17 total score (p=0.30).

3.2 Quality of Life Changes

Overall, there were no statistically significant changes in QoL assessments in the total FACT-G score and subscales (physical, social, functional well-being and neurotoxicity) except for emotional well-being which improved (median score 18.0 versus 19.1 at baseline and 6-months respectively, p=0.02) as shown in Table III. There were no significant differences found in QoL assessments between patients in the SCT versus non-SCT cohort (Appendix Table IIA). Using the MID cut off of 5, the majority of patients 25/36 (69.4%) patient showed a stable or improved QoL as measured by the FACT-G [11/16 (68.8%) and 14/20 (70.0%) in the SCT and non-SCT group respectively]. Similarly, using the MID cut-off of 2.5 for Ntx subscale, 24/36 (66.7%) patients had stable or improved symptoms [11/16 (68.8%) and 13/20 (65.0%) in the SCT and non-SCT group respectively].

Discussion

Overall, our study demonstrates that a cohort of 36 older adults with newly-diagnosed MM initiating treatment did not experience statistically significant impairment in geriatric domains or deterioration in functional status or overall QoL at 6-months of follow-up, as compared to baseline. Treatment was associated with improved overall mental health well-being. Additionally, using MID threshold, the physical performance measure TUG test improved in a subset of individuals.

The value of a geriatric assessment of adults with MM is increasingly being recognized [25, 26]. Various tools including post hoc algorithms have been developed to assess the frailty status of patients with MM at baseline[27]. Additionally, clinical trials designs in MM are now being developed based upon this baseline frailty assessment[28]. Unfortunately, there is a paucity of data in MM about how these geriatric domains change over time and the clinical implication of that change. In other hematological malignancies, such as acute myeloid leukemia, longitudinal geriatric assessment is known to be dynamic, with physical function declining significantly after induction chemotherapy, whereas cognitive function remains

stable and emotional health improve[29]. In leukemia, disease status is also known to impact serial geriatric assessments with global QoL, fatigue, mood, and physical performance measures all improving in patients who achieve disease control [30]. To our knowledge, there has only been one prior study conducted in MM with serial geriatric domains measures conducted by Rosko *et al.* This study was limited to patients undergoing SCT and therefore had an overall 'younger' population, with a median age of 60 years. This study did not show any significant changes in geriatric domains in patients pre- and post-transplant [4]. As compared to the study by Rosko *et al.*, we aimed to assess the changes in geriatric domains specifically in older adults with MM and both in patients undergoing SCT or not. Our study adds meaningfully to the existing, quite limited literature on this subject, and may inform decision making for both patients and clinicians about the trajectory of functional status and QoL as older adults undergo treatment for MM over 6-months following initial diagnosis.

With respect to geriatric domains, we observed a statistically significant improvement in psychological status with treatment. This is consistent with other data in hematological malignancies which shows improvement in mental health status following treatment [29, 31] Interestingly, in our study, this improvement in mental health status did not differ among those individuals that had improvement versus stable physical performance, suggesting that patients in general had improved mental health status with treatment regardless of their physical function. Many of the other measured geriatric domains showed no significant change, which is re-assuring that older patients did not experience clinical deterioration despite treatment. Body mass index declined in patients that underwent SCT; however, it is unknown whether that may have subsequently risen with longer follow-up, or it is also possible that weight loss was intentional and hence not a marker of some form of clinical decline. Overall, although this is a small study, it provides a preliminary answer to the clinical questions often posed by 'real-world' patients with myeloma about how their functional status is likely to evolve as they initiate treatment. Furthermore, there is a small group of older adults with MM that remain untreated [32, 33]. Although the reasons for this remain unclear and likely includes a number of multifactorial reasons, fear of functional decline and QoL, are known to influence older adults decision to potential reject cancer treatment[34]. Our data may provide individual patients and clinicians with further information regarding potential functional and QoL trajectory as they consider treatment approaches.

Furthermore, although SCT patients are known to be 'more fit' as they are younger, with fewer co-morbidities, better functional status, and faster performance on the Timed Up and Go in this cohort[11], the trajectory and change in parameters between baseline and 6-months of follow-up did not significantly differ among patients that underwent a SCT or did not undergo a SCT. This is also clinically relevant for older adults who may struggle about decisions regarding specific SCT versus non-SCT based treatment options and their potential implications on functional status.

With regards to physical performance measures, in our cohort, the TUG showed a trend towards improvement over a period of 6-months. Additionally, most patients either improved or remained stable using the MID for TUG suggesting that treatment does not impair patient's physical performance status or potential frailty. The prognostic value of a simple

physical performance such as a 4-meter walk test are increasingly being recognized in hematological malignancies[35]. Of note, subsequent to the inception of this study, it was shown that TUG may not add prognostic or predictive information beyond gait speed, suggesting that future studies should use gait speed due to its ease of administration[36]. As gait speed can change over time, it may also prove to be a measure of a change in frailty over time and further studies will be required to evaluate this finding.

Lastly, our study also evaluated QoL in patients with MM and showed that, using validated MID thresholds, most patients reported an improvement in or at least stable overall QoL. Additionally, emotional well-being also showed statistical improvement. Although QoL is increasingly being incorporated into clinical trials[37–40], there is a paucity of data in 'real-world' patients. A previous cross-sectional registry study showed that adults with MM experienced significantly worse QoL compared to other cancers [41]. Factors associated with poor QoL include being older, female gender, financial stressors, psychological morbidity, and low physical activity[42–44]. In comparison to these cross-sectional studies which only capture information at one specific time point, our study used longitudinal assessment of QoL over a period of 6-months to show that most patients in fact improved or remained stable over time. Knowledge of this information is significant as it may inform shared decision-making regarding treatment for older patients who may prioritize QoL in their oncologic management[28].

Strengths of our study include longitudinal assessment of geriatric domains and QoL in older adults with MM undergoing both SCT or not, which represents the first study done in this area. Our study was limited by the short follow-up period of 6-months, as it is unknown how these parameters might change with a different follow-up schedule or with longer follow-up. There is some suggestion from clinical trial data that QoL deterioration occurs immediately post transplantation and recovers 1–2 months post-transplant [45], with further improvements occurring with longer period of follow up[38]. Although the FACT-G is a well-validated tool, it is not a myeloma-specific QoL assessment tool for which the MID is defined specifically for the MM cohort, such as the EORTC QLQ-MY20[46]. Therefore, it is possible that it may not have captured all of the symptoms associated specifically with MM and regimen toxicity. Finally, it is possible that a moderate effect on overall QoL might be present in this population, but were not found to be statistically significant in this study due to the small sample size available. Further, we were unable to conduct subgroup analysis to determine how disease response and additional toxicities may have affected overall QoL and geriatric domains; however, previous studies have shown an association between better QoL and disease control [47].

In conclusion, our study demonstrates that for older patients with MM undergoing treatment, both geriatric domains and overall QoL do not significantly deteriorate over time and, in fact, overall mental health well-being improves. Additionally, a physical performance measure such as a gait speed may provide a more dynamic and longitudinal assessment of frailty, which needs to be confirmed in larger studies.

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Appendix

Table IA:

Change (median, range) in selected geriatric domains from baseline to 6 months following diagnosis

Characteristic	Non-SCT N=20	SCT N=16	P-value
Body Mass Index kg/m^2	0.47 (−3.9, 3.8)	−1.59 (−6.9, 2.8)	0.04
Karnofsky performance status	0 (−20, 40)	0 (−20, 20)	0.25
Number of dependent IADL domains	0 (−5, 6)	0 (−4, 6)	0.73
Number of Medications	1 (−5, 8)	−2 (−6, 11)	0.15
Psychological status: Mental Health Inventory-17 Total score	6.3 (−19.0, 53.9)	3.7 (−11.2, 26.5)	0.23
Cognition: Blessed Orientation Memory Concentration Test Score	0 (−8, 8)	0 (−6, 6)	0.58
Medical Outcomes Study: Patient limited in moderate activity (N, %)			0.43 *
Declined	5 (25.0)	2 (12.5)	
No change	13 (65.0)	12 (75.0)	
Improved	2 (10.0)	2 (12.5)	
Number of falls	0 (−6, 3)	0 (−1, 1)	0.74
Timed up and Go Test secs	−1.8 (−10.2, 2.7)	0.1 (−7.6, 1.8)	0.38

* comparison is improved/no change versus declined

Table IIA:

Change (median, range) in quality-of-life parameters from baseline to 6 months following diagnosis

Characteristic	Non-SCT N=20	SCT N=16	P-value
Physical Well Being	−2 (−13, 14)	1 (−4, 19)	0.29
Social Well Being	0 (−14, 7)	0 (−11, 8)	0.97
Emotional Well Being	1 (−9, 6)	1 (−3, 7)	0.76
Functional Well Being	1 (−7, 13)	1.5 (−6, 25)	0.80
Neurotoxicity	0 (−32, 18)	0.5 (−11, 14)	0.69
FACT-G Total Score	2 (−27, 30)	6.9 (−16, 32)	0.66

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Table I:

Baseline characteristics of cohort

	N=36
Age (median, range)	70 (65–84)
Male Gender (N, %)	24 (66.6%)
Race (N, %)	
Caucasian	28 (77.7%)
Black	6 (16.6%)
Other	2 (5.6%)
Charlson Co-morbidity Index (N, %)	
0	18 (50.0%)
1–2	14 (38.8%)
3 or more	4 (11.1%)
Treatment prior to 6-month follow-up (N, %)	
SCT	16 (44.4%)
Non-SCT	20 (55.5%)
Bortezomib containing regimen (N,%)	27 (75.0%)
ISS stage (N, %)	
1	11 (30.5%)
2	12 (33.3%)
3	9 (25.0%)
Unknown	4 (11.1%)
High Risk Cytogenetics (N, %) (4;14 and 17p)	8 (22.2%)
Overall Response Rate *	
VGPR or better	8 (22.2%)
Partial response or less	23 (63.8%)
Progressive disease	3 (8.3%)
Unknown	2 (5.6%)
Overall Survival (1 yr, 95% CI)	87.9% (70.9–95.3%)

ISS International Staging System; SCT autologous stem cell transplant; VGPR very good partial response

* Defined as the best response during assessment period of 6-months

Table II:

Change in Geriatric Domains over a period of 6-months (median, range)

Characteristic	N (baseline, 6 months)	Baseline	6 months	Change Baseline to 6 months	P-value
Body Mass Index (kg/m^2)	40, 34	29.4 (16.3,39.3)	27.3 (18.5,42.4)	−0.5 (−6.9,3.8)	0.36‡
Karnofsky performance status	40, 33	80 (50,100)	80 (40,100)	0 (−30,40)	0.15‡
Number of Medications	39, 28	9 (1,23)	9 (4,25)	1 (−6,18)	0.54‡
Number of dependent IADL domains	40, 36	2 (0,11)	1 (0,8)	0 (−5,6)	0.83‡
Psychological status: Mental Health Inventory-17 Total Score	40, 34	77.1 (31.8,96.5)	84.3 (53.9,100)	6.0(−19.0,53.9)	<0.001‡
Cognition: Blessed Orientation Memory Concentration Test Score	40, 34	2 (0,22)	1 (0,14)	0 (−8,8)	0.22‡
Medical Outcomes Study Patient limited in moderate activity (N, %)	40, 36				0.73†*
Not at all		11 (27.5%)	11 (30.5%)		
Limited a little		10 (25.0%)	10 (27.7%)		
Limited a lot		19 (47.5%)	15 (41.6%)		
Improved / Stable at 6 months				32 (88.9%)	
Worsening at 6 months				4 (11.1%)	
Number of falls (N,%)	39, 35				0.39†
0		28 (71.8%)	29 (82.9%)		
1 or more		11 (28.2%)	6 (17.1%)		
0 falls baseline / 0 6 months				20 (58.8%)	
0 falls baseline / 1+ 6 months				4 (11.8%)	
1+ falls baseline / 0 6 months				8 (23.5%)	
1+ baseline / 1+ 6 months				2 (5.7%)	
Timed Up and Go Test#, seconds	35, 28	12.3 (7.3–33.5)	11.0 (6.2–23.4)	−0.7 (−10.2, 2.7)	0.057‡

IADL Instrumental Activity of Daily Living

†McNemar test comparing Not at all vs At least some limitation, or 0 vs 1+ falls

‡Wilcoxon rank sum test of whether the change score compared to baseline equals 0

*based on not at all versus limited a little/lot

#Calculated only for patients able to complete the Timed Up and Go Test unassisted

Table III:

Changes in Quality of Life over a period of 6-months (median, range)

	N	Baseline	6 months	Change	P-value
Physical Well Being	40, 36	21.0 (4,28)	20.0 (9,28)	0.5 (−13,19)	0.69
Social Well Being	40, 36	24.0 (13,28)	24.5 (7,28)	0 (−14,8)	0.71
Emotional Well Being	40, 36	18.0 (6,24)	19.1 (10,24)	1 (−9,7)	0.02
Functional Well Being	40, 36	15.7 (1,28)	20.5 (3,28)	1 (−7,25)	0.11
Neurotoxicity (Ntx)	40, 36	37.0 (2,44)	36.0 (12,44)	0 (−32,18)	0.53
FACT-G Total Score	40, 36	75.0 (39,104)	85.4 (42.7,104)	3.5 (−27,32)	0.16

FACT-G Functional Assessment of Cancer Therapy; Ntx neurotoxicity subscale