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Use of a Comprehensive Frailty Assessment to Predict Morbidity in Patients with Multiple Myeloma undergoing Transplant

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Abstract

Multiple myeloma (MM) is a disease of aging adults and autologous stem cell transplant (ASCT) is considered the standard of care. As the population ages a growing number of older adults will undergo ASCT and an objective approach to estimate physiologic reserve and transplant morbidity risk is warranted. Here, we evaluate assess *p16^{INK4a}* (*p16*), a molecular aging biomarker, along with geriatric metrics to determine risk of transplant toxicity.

Methods—We prospectively evaluated 100 MM patients for frailty before and after ASCT using a Geriatric Assessment (GA) and collected T-cells for analysis of p16 using a custom nanostring codeset.

Results—Pre-transplant physical function was predicative of hospital length of stay (LOS). Each one-unit increase in physical function score, the average LOS decreased by 0.52 days (95% CI, –1.03–0.02); $p=0.04$). Similarly, higher self-report of ADL/IADL (Human Activity Profile) was associated with shorter LOS (0.65 less days (95% CI –1.15– –0.15), $p=0.01$). Patients with anxiety/depression (OR= 1.10 (95% CI 1.00–1.22), $p=0.056$), lower handgrip strength (OR=0.90 (95% CI 0.82–0.98), $p=0.02$), falls (OR=1.60 (95% CI 1.07–2.38), $p=0.02$), or weight loss (OR=5.65 (95% CI 1.17–25.24), $p=0.03$) were more likely to be re-admitted. The estimated EFS at

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1-year was 85% (95%CI, 75–91) with median follow-up of 15.7 months. Weight loss was a significant predictor of EFS (HR=3.13 (95%CI 1.15–8.50), $p=0.03$). Frailty assessment by self-reported fatigue minimally correlated with T-cell *p16* expression ($r=0.28$; $p=0.02$). Age, Karnofsky Performance Status (KPS), or Hematopoietic cell transplantation-specific Co-Morbidity Index (HCT-CI) did not predict hospital LOS or readmissions.

Conclusions—Our data illustrate that a GA can identify individuals with MM who are at greater risk for morbidity following ASCT.

INTRODUCTION

The leading indication for autologous stem cell transplant (ASCT) in the United States is a diagnosis of multiple myeloma (MM).¹ ASCT, along with novel therapies, has doubled the 5-year survival of MM patients from 25% in the 1980's to nearly 50% in the modern era.² ASCT is considered the standard-of-care for eligible patients; however, transplant eligibility is subjective, relying on a clinicians' estimate of perceived patient physiologic reserve and resilience.³ Historically, patients under 65 years of age, with good performance status and minimal comorbidities were eligible for ASCT. With improved supportive care over time, there is an increasing number of older adults undergoing ASCT. Currently 44% of patients who receive ASCT are now > 60 years of age.¹ As the myeloma population ages, quantitative approaches to assess patient health status are needed to reduce therapeutic toxicity and transplant morbidity. A valuable tool to identify frailty and resolve occult health factors is a Geriatric Assessment (GA).

A GA is a global evaluation of the health of older adults, comprising a multi-dimensional evaluation of functional status, fall history, social support, cognitive and psychologic status, sensory loss, nutritional status, and co-morbidities. GA tools have established metrics to categorize limitations in geriatric domains and have been shown to accurately assess the risk of morbidity and mortality in cancer populations and to identify frailty.^{4,5} In patients with solid tumors or allogeneic transplant recipients, GAs predict mortality and toxicity independent of performance status and age.^{6,7} While it is established that a GA can improve outcomes in patients with cancer, feasibility, practicality, and disease specificity are barriers to implementation in MM.^{8–10}

Development of a peripheral blood test to mark physiologic frailty would be a powerful tool for the field of geriatric oncology, allowing for vulnerable individuals to be rapidly and reproducibly identified. Many candidate biomarkers are being explored to estimate physiologic reserve and risk for chemotherapy and/or transplant toxicity.¹¹ In particular, there is considerable interest in measuring *p16^{INK4A}* (p16), one of the most robust and validated aging biomarkers, in patients with cancer.¹² p16 functions to inhibit cell-cycle progression when cells are exposed to a variety of internal and external stressors.^{13–17} Prolonged expression of *p16* promotes an irreversible cell cycle arrest, termed cellular senescence. *p16* accumulates with age in a variety of human tissue types and rises more than 16-fold in peripheral blood T-cells (PBTL) over the human lifespan.^{18,19} The need for objective biomarkers of physiologic age is especially important in the MM population due to the age of affected individuals, heterogeneity of fitness in older adults, and diverse treatment

strategies available. In younger patients, ASCT mortality is less than <1%, yet many older adults are deemed ineligible for transplant due to concerns of tolerability and morbidity. Here, we prospectively examined the hypothesis that a GA and T-cell p16 measurements in a MM population would predict transplant morbidity assessed by hospital re-admissions or death, length of stay (LOS), and event-free-survival (EFS).

METHODS

Patients

We performed a prospective cohort study at a single institution consisting of 100 patients 18 years old, with a plasma cell dyscrasia and intention to undergo ASCT. Patients were approached consecutively and age was not used to determine geriatric status from April, 2014 through October, 2015 to participate in a GA study which consisted of demographic data, self-report assessments, and healthcare provider-administered metrics. The GA was completed at the pre-transplant visit and 90 days post-transplant. A peripheral blood sample was also obtained at these time points. The study was approved by the Institutional Review Board of The Ohio State University and written informed consent was obtained for all patients in accordance with Declaration of Helsinki.

Geriatric Assessment Metrics

A 4-question nutritional survey was used to assess weight gain and/or loss. The Brief Fatigue Inventory (BFI) was used to evaluate severity and impact of cancer-related fatigue.²⁰ Responses to the BFI were recorded on a 10-point scale and averaged to give a composite score (1–3 mild, 4–6 moderate, 7+ severe). The Human Activity Profile (HAP) was used to evaluate activities of daily living (ADL) and instrumental ADL(IADL) including relatively minor changes in physical function, has been validated in bone marrow transplant population,²¹ and is a robust assessment of ADL/IADL. In our study the HAP included a list of 93 specific and detailed ADL and IADL ranked according to the energy expenditure required to perform each task (e.g. ADL such as dressing self to higher level functioning cooking, cleaning, jogging, bicycling, swimming). The HAP-Maximum Activity Score (MAS) represented the number of difficult tasks the respondent is “still doing,” and the Adjusted Activity Score (AAS) was calculated by counting the number of activities the respondent has “stopped doing,” and subtracting that from the MAS (higher score indicated a higher activity level). The Hospital Anxiety and Depression Scale (HADS) was used to assist in the evaluation of psychological status by detecting clinically significant depression and anxiety.²² Patients responded to this 14-item scale in which 7 items measured anxiety and 7 items measured depression (0–7 “not present”, 8–10 “borderline”, 11+ “definite”). The Medical Outcomes Study-Social Support Survey (MOS-SSS) assessed individuals perceptions of the availability of different categories of social support; emotional, informational, tangible, positive social interaction, and affection.²³ Subscale scores for each of these domains were calculated, as well as the total score (range 0 to 100 higher scores indicated greater perceived social support). Cognitive function was evaluated using the Modified-Mini-Mental Status (3MS) (range 0–100).²⁴ The Short Physical Performance Battery (SPPB) was designed to evaluate balance, strength, and gait speed (range 0–12, higher scores represent higher physical function).²⁵ Dominant and non-dominant handgrip

strength was assessed on a hydraulic hand dynamometer. Scores were continuous variables measured in kilograms and were analyzed based on the patient's age, gender and dominant versus non-dominant hand.

Molecular Markers

Patients enrolled had PBTL collected for mRNA analysis before transplant and 90-days post-transplant. CD3+ T-cells were isolated using RosetteSep reagents (StemCell Technologies, Vancouver BC). RNA was extracted using RNeasy Plus Mini Kit (Qiagen, Valencia CA) and analyzed using a custom nanostring codeset [OSU_Senescence] which includes detectors for cellular senescence (*CDKN2A/p16*) and standard housekeeping genes (GUSB, HPRT1, PGK1, UBC, YWAZ). Housekeeping genes of varying overall expression levels were selected based upon their relative stability in T-cells, which was confirmed in our analyses.

Statistical considerations

Patient's clinical characteristics and GA scores were summarized using descriptive statistics, and compared between pre and post-transplant observations using Wilcoxon signed rank test or McNemar's test. Spearman rank correlation coefficients were used to examine the strength of relationships between p16 and GA scores. The associations between GA scales and ASCT-related morbidity endpoints including 90-day hospital readmission, LOS and EFS were estimated using generalized linear models or proportional hazards model. EFS was calculated from transplant date until clinical relapse or death, whichever occurred first, censoring patients at the time last known to be event-free. For hospital readmission, given few events, only univariable modeling analyses were performed for each GA scale. For LOS and EFS, univariable models were first fit for each GA scale, then multivariable models were built using forward selection ($p < 0.05$) to control for other important clinical covariates including age, Karnofsky Performance Status (KPS) and Hematopoietic Cell Transplantation-specific Comorbidity Index (HCT-CI)

RESULTS

Clinical Demographics

A prospective cohort of 100 patients with plasma cell dyscrasia (MM=93, AL Amyloidosis=6, POEMS=1) were evaluated for ASCT at a single institution and underwent a GA between April, 2014 and October, 2015. The GA was completed a median of 30 days prior to ASCT (range 7–140 days) and a second GA was completed 90-days post-transplant. A second GA was completed for n=61 (70%) of evaluable patients (Figure 1). 26 patients did not complete a second GA due to scheduling or patient preference; there was no significant difference in baseline geriatric metrics among those who did and did not undergo a second GA (data not shown). At baseline, patient median age was 59.5 years (range 36–75) patients were approached consecutively and age was not used to determine eligibility for study or for geriatric assessment status. Most had early stage disease (International Staging System (ISS) Stage I 49%), and were in a partial remission (PR) or better at the time of transplant [stringent or/Complete Remission (10%), Very Good Partial Remission (VGPR) (31%), PR (31%)]. In the enrolled population, induction followed by transplant was the first

line of therapy for most patients (77%), and patients were evenly divided among triplet and doublet therapy (52% vs. 48%, respectively), exhibiting preserved organ function (Table 1).

Geriatric Assessments

GA impairments before and after transplant are outlined in Table 2. At baseline, using spearman correlation coefficient there was a minor relationship with social support (MOS-SSS) and age ($r=0.25$, $p=0.01$) but no age relationships with any other geriatric domains. Prior to transplant, deficits in geriatric domains were prevalent, most patients reported some deficits in ADL/IADL with median HAP MAS scores of 73 (range 20–94) and AAS of 64 (range 18–94). Most patients reported moderate fatigue prior to transplant median score 4.6 (range 0–9.8). Median hand-grip scores by age and gender meet the threshold of impairment by published grip strength normals that are less than the lower limit 95% confidence intervals (CI).²⁶ After ASCT, most patients lost weight (pre 195.5 lbs. vs. post 189 lbs.; $p<0.01$) and showed deficits in performance status by physician reported-KPS (pre KPS 90=52% vs. post KPS 90=32%; $p=0.02$). Fatigue was moderate prior to transplant and improved post-ASCT (pre median=4.6 vs. post median=2.9; $p=0.003$). Self-report of physical function was variable (HAP MAS pre median=73 vs. post median=64; $p=0.71$), however, objective measurements of physical function by handgrip showed a post-transplant decline for most patients [Non-dominant (female pre median=20kg vs. post median=16kg; $p=0.004$) (male pre median=33kg vs. post median=30.5kg; $p=0.05$). One-third of patients reported clinically borderline or case definite levels of anxiety both before and after transplant [pre $n=30$ (30%) vs. post $n=19$ (31%)]. Nearly one-fifth ($n=19$) of patients screened positive for depressive symptoms prior to transplant and 11% ($n=7$) post-ASCT. Patients generally had adequate to high levels of social support (MOS-SSS) and had no cognitive deficits by 3MS both before and after transplant.

Clinical Outcomes

The median hospital LOS for transplant was sixteen days (range 12–36). Fifteen percent ($n=13$) of patients were re-admitted within 90-days from transplant. At the time of discharge from transplant, one in four patients required additional needs (home health $n=5$; home physical therapy $n=7$, skilled nursing facility $n=2$, hospice $n=1$). Table 3 illustrates the relationship of clinical variables, geriatric metrics, and p16 with transplant LOS and 90-day hospital readmissions/death. Using univariable modeling, hospital LOS was associated with pre-transplant physical function metrics including SPPB score (0.52 fewer days (95% CI –1.03–0.02); $p=0.04$) and self-report of physical function (HAP AAS 0.65 fewer days (95% CI –1.15–0.15), $p=0.01$; HAP MAS 0.54 fewer days (95% CI –1.08–0.01), $p=0.05$). With each one unit increase in SPPB pre-transplant, indicating better physical function, the average LOS during transplant dropped by 0.52 days (Figure 2). In multivariable analysis, once HAP AAS was accounted for, no other variable provided additional prognostic information. Patients with anxiety and depression (HADS Odds Ratio (OR) = 1.10 (95%CI 1.00–1.22), $p=0.056$), lower handgrip strength (OR=0.90 (95%CI 0.82–0.98), $p=0.02$), lower self-report of physical function (HAP AAS OR=0.66 (95%CI 0.45–0.95), $p=0.03$), falls (OR=1.60 (95%CI 1.07–2.38), $p=0.02$), and self-report of pre-transplant weight loss (OR=5.65 (95%CI 1.17–27.24), $p=0.03$) were more likely to be re-admitted to the hospital following transplant. The estimated EFS at one year was 85% (95% CI, 75–91) with a

median follow-up of 15.7 months. The median EFS has not been reached, 22 events have occurred in 88 evaluable patients (nineteen relapses, three deaths related to disease progression or complications). When analyzing the relationship between EFS and geriatric metrics, weight loss (prior to transplant) emerged a significant predictor of EFS (Hazard Ratio (HR) =3.13 (95% CI 1.15–8.50), $p=0.03$) and was the only variable of significance by multivariable analysis after forward selection. Age was analyzed as predictor of EFS and it was not associated with EFS ($p=0.72$). In univariable analysis, better handgrip strength (non-dominant) was associated with lower risk of death HR 0.91 (95% CI 0.83–0.99), $p=0.03$). Similarly, patients with higher function by self-report (HAP AAS) were at borderline significance for lower risk of death, HR 0.69 (95% CI 0.47–1.02, $p=0.06$).

p16 Molecular Markers and Frailty Phenotype

The relationship between molecular markers of cellular senescence in PBTLs and frailty metrics was examined (Table 4). PBTLs were isolated pre-transplant and assessed for mRNA expression using a custom Nanostring Codeset (OSU_Senescence). Pre-transplant self-report of fatigue, measured by BFI scales, had a minimal effect correlation with *p16* expression ($r=0.28$; $p=0.02$) in pre-transplant patients (Figure 3). Furthermore, there was no relationship of *p16* with other geriatric domains. *p16* expression also had no relationship with hospital LOS, 90-day readmission, or ongoing EFS analyses.

DISCUSSION

Herein, we investigated the prognostic significance of a GA in MM patients prior to ASCT. Our findings reveal that vulnerable transplant populations can be identified with use of a GA to detect age-related health factors that result in longer LOS and hospital readmissions. Using a comprehensive approach, we have identified four factors that place MM transplant patients most at risk: physical function, weight loss, anxiety and depression. While study participants were deemed fit for transplant there was significant heterogeneity in terms of health recovery after transplant. At discharge, one in four patients required additional needs and 15% of patients were re-admitted within 90 days. Consistent with data from other publications,^{27,28} anxiety and depression were prevalent both before and after transplant and, as we report herein, anxiety and depression levels were significantly associated with hospital readmission. In our study, patients with weight loss prior to transplant, were five times more likely to be admitted to the hospital. Readmission was also associated with anxiety, depression, and a fall history. Assessing patients using GA domains to identify frailty is increasingly recognized in older adults,²⁹ however frailty is prevalent in younger cancer survivors and associated with an increased risk of mortality in young hematopoietic cell transplant populations.^{30,31} Our study illustrates how a GA can both identify health differences and detect dynamic health changes before and after transplant in patients of all ages.

Using a GA, we identified geriatric deficits that clearly influenced morbidity in the MM ASCT population and are potentially modifiable in the peri-transplant period. Hospital LOS and readmissions are known to be related to mortality in the bone marrow transplant population.³² In particular, physical function was predictive of hospital LOS using the SPPB

screening tool and by self-report. Consistent with prior work,³³ patients who lost functional independence showed high rates of morbidity, disability and mortality. As functional decline is amplified in patients with cancer and is a predictor of early death,^{34,35} our work suggests the use of objective performance tests as powerful predictors of functional decline in high risk populations, such as the bone marrow transplant recipients. An important limitation of our study is recognizing that our population of patients undergoing transplant were selectively consecutively and were not all newly diagnosed myeloma patients undergoing first transplant. Patients received variable induction regimens, with various depths of response, and a quarter of our population received more than one line of therapy. This is important to recognize given that functional differences may be evident based on disease treatment strategies and duration of therapy. The SPPB tool is one of the most robust measures for assessing risk of death, where each 1-unit increase predicts a 12% reduction in mortality in cancer survivors.³⁶ In our study, each 1-unit change in SPPB score decreased hospital LOS by half a day and identified at risk patients pre-transplant. Standard tools to measure patient fitness such as age and KPS had no relationship with hospital LOS, readmissions or EFS in our analysis. Self-report measurements of function such as the HAP AAS/MAS are robust and account for what patients have “stopped doing”. In our study, these scores were predictive of both LOS and hospital readmission. Future studies are warranted to risk stratify patients to transplant based upon fitness, to determine if factors such as deconditioning are reversed that transplant morbidity could be ameliorated.

Our data suggest that objective tools, such as the SPPB or handgrip dynamometers more consistently identify patients at risk for hospital readmissions and longer LOS, than other measures of frailty such as KPS or HCT-CI. Of critical importance, a GA identifies deficits in the MM patient population that can be improved (i.e. physical function and weight loss) prior to transplant. Physical deconditioning is often recognized, but rarely addressed in pre-transplant patients. In recent years, the perspective on physical activity has changed significantly in patients with cancer, and many reports document the benefit of exercise in this population.^{37–39} Physical fitness is highly predictive of survival in patients with cancer,³⁶ yet, exercise regimens and physical therapy programs to prevent deconditioning in hematologic malignancy populations are conflicting.^{40–42} Nutritional deficits and weight loss are multifactorial in a cancer population, and are related to disease, treatment, and cancer-associated cachexia. Prior studies show that nutritional status is an independent predictor of early death in older adults⁴³ and patients with cancer³⁵ receiving first line chemotherapy. Here, we report that weight loss is profound in post-transplant MM patients and related to hospital readmissions and EFS. Although clear pre-transplant nutritional interventions have not been studied in MM, such programs can improve weight, quality of life and performance status in other cancer populations.^{44,45} Unfortunately, patient- or prescriber- driven dietary modifications are highly variable, given that supplement use is widespread and nutritional interventions, short of TPN use, are underreported in transplant.⁴⁶ Nevertheless, our data suggest that in the future timing of transplant could be altered to allow a patient’s nutritional status to stabilize prior to such an intensive intervention.

Aging biomarkers are being explored as rapid and quantitative means to measure physiologic fitness and predict life expectancy.^{47–49} Personalizing cancer therapy based on physiologic reserve could be used in a multitude of clinical scenarios in which biologically

younger individuals would be prescribed a more intensive therapy with higher potential benefit. This quantitative approach would resolve the under treatment of older adults with cancer due to fear of adverse toxicities and also identify patients who are subjected to more aggressive therapies and suffer morbidity and mortality. To our knowledge, we are the first to report the comparison of *p16* with a frailty phenotypes determined by a GA in an oncology population. Within our sample population we show limited relationship with fatigue and no relationship with clinical outcomes or other more objective markers of physical function, such as the SPPB or handgrip. In contrast, *p16* is known to be associated with frailty metrics such as hand-grip strength in a community dwelling population.⁵⁰ Moreover, *p16* measurements have been successfully implemented in the setting of kidney allografts, where increased *p16* is associated with renal ischemia related to reperfusion time^{51,52} and is predictive of post-transplant allograft function.⁵³ However, others have shown that *p16* has no relationship with frailty metrics or hospital LOS in adults undergoing cardiovascular procedures.⁴⁹ It is possible that measurement of *p16* in the hematopoietic graft might better predict MM outcomes as increases in this biomarker are cell-type specific.¹⁷ Alternatively, lack of a baseline *p16* measurement prior to induction therapy may hinder our ability to predict transplant outcome; however, we have previously demonstrated that *p16* is not affected by lenalidomide-based chemotherapy.⁵⁴ We have previously reported, that *p16* significantly increases post-transplant and expression is durable many years out which may be more reflective of long-term health outcomes.⁵⁴ Future study of *p16* in a larger population, or a more homogeneous population, may help clarify the relationship between this biomarker and physiologic age and/or frailty. Our study is limited by the single-center design of our study and we have yet to validate the GA and/or interventions to determine if these metrics and/or interventions could mitigate transplant morbidity.

Our results provide the clinician with tools such as the SPPB, handgrip and self-report of function to aid in the transplant decision making process and to prevent morbidity in the MM population. Our data have demonstrated that a comprehensive approach can yield modifiable factors that can be improved upon prior to transplant. Future directions include embedding physical therapy, robust nutritional assessment and screening for anxiety and depression as routine measures for transplant care. Based upon this preliminary work, we have continued to use the SPPB in our ongoing interventional assessments and streamlined our GA evaluations to be more consistent with other published literature in geriatric oncology¹⁰ with use of the Cancer and Aging Research Group GA for active investigations of frailty in the malignant hematology population.⁵⁵ As such active studies evaluating the feasibility of exercise in high risk patients to improve physical function and quality of life is underway (NCT02791737). Our institutional Geriatric Hematology clinic is a multi-disciplinary team of providers (physical therapist, pharmacist, nutritionist, RN case manager, audiologist, nursing cognitive assessment, and oncologist) to identify and optimize health factors for older adults and vulnerable populations (e.g. transplant populations). As the population ages, clinicians need quantitative approaches to recognize differences in health status and prevent longer hospital stays and readmissions. Biomarkers of aging, such as *p16*, cannot fully characterize the complexity of frailty in all patients and further work to understand the biology of aging is necessary to ascertain underlying health status in the oncology population. Our data illustrate that the differences in clinical outcomes in pre-

transplant MM patients may be predicted and managed with the use of a geriatric assessment to identify and resolve occult factors that contribute to morbidity.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.
Schema of Geriatric Assessment in patient cohort before and after autologous stem cell transplant

Figure 2.

The Short Physical Performance Battery (SPPB) was administered to 88 patients prior to autologous stem cell transplant. For each one unit increase in SPPB, the transplant hospital length of stay decreased by 0.52 days.

Figure 3. Pre-transplant self-report of fatigue, measured by the Brief Fatigue Inventory had a minor correlation with *p16* expression ($r=0.28$; $p=0.02$)

Table 1

Pre-Transplant Clinical Demographics

n=100	
Age, median (range)	59.5 (36–75)
Gender, no. (%)	
Female	40 (40)
Male	60 (60)
Histology, no. (%)	
MM	93 (93)
AL Amyloidosis	6 (6)
POEMS	1 (1)
International Staging System (ISS) *, no. (%)	ISS
1	38 (49)
2	23 (30)
3	16 (21)
Pre-Transplant Disease Status, no. (%)	
stringent complete Response (sCR)	1 (1)
Complete Response (CR)	8 (9)
Very good partial response (VGPR)	27 (31)
Partial response (PR)	27 (31)
Stable disease (SD)	8 (9)
Progressive disease (PD)	9 (10)
Not evaluable (NE)	8 (9)
N/A or Unknown	12
Number of Regimens, median (range)	2 (1–11)
Induction Therapy, no. (%)	
cytoxan, lenalidomide, dexamethasone (CRd)	2 (2)
cytoxan, bortezomib, dexamethasone (CyBorD)	27 (27)

bortezomib, lenalidomide, dexamethasone (VRd)	23 (23)
lenalidomide, dexamethasone (RD) [‡]	13 (13)
thalidomide, dexamethasone (TD)	2 (2)
bortezomib, dexamethasone (VD)	33 (33)
Lines of Therapy, no. (%)	
One line	77 (77)
More than one line	23 (23)
B2M mg/L, median (range, unknown) ^{‡‡}	
	2 (1.1–50, 9)
Creatinine mg/dL, median (range, unknown) ^{‡‡}	
	0.9 (0.6–11.2, 0)
Albumin g/dL, median (range, unknown)	
	4 (0.1–4.8, 1)
WBC K/ul, median (range, unknown)	
	5.3 (1.8–23.8, 1)
Hemoglobin g/dL, median (range, unknown)	
	12.3 (6.6–15.3, 1)

^{*} 23 patients NA or Unknown ISS Stage

[‡] Includes one patient who was treated with lenalidomideRevlimid alone

^{‡‡} Includes End Stage Renal Disease

Multiple Myeloma (MM); Polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, skin changes (POEMS)

Table 2

Change in Geriatric Metrics Pre and Post-Transplant

Geriatric Assessment Metrics		Pre-transplant n=100	90 day post-transplant n=61	p-value
Nutrition: median (range, unknown)				
Weight (lbs.)		195.5 (98–362, 2)	189 (103–339, 0)	<0.001
BMI		29.7 (17.1–48.3, 11)	30.3 (20.6–47.5, 13)	0.001
Physician Reported Physical Function: no. (%)				
KPS				
70%	20 (22)	19 (32)		0.02
80%	24 (26)	21 (36)		
90%	33 (36)	13 (22)		
100%	15 (16)	6 (10)		
Unknown	8	2		
Self-Report Physical Function: median (range) or no. (%)				
HAP MAS	73 (20–94)	64 (5–91)		0.71
HAP AAS	64 (18–94)	70 (5–92)		0.70
Fatigue – BFI				
median (range)	4.6 (0–9.8)	2.9 (0–7.1)		0.003
mild (1–3)	42 (42)	42 (69)		
moderate (4 – 6)	46 (46)	18 (30)		
severe (7+)	12 (12)	1 (2)		
Objective Physical Function: median (range) or no. (%)				
Handgrip dominant				
female	21.5 (10–44)	18 (12–40)		<0.001
male	38 (12–72)	32 (16–72)		
Handgrip non-dominant				

Geriatric Assessment Metrics	Pre-transplant n=100	90 day post-transplant n=61	p-value
female	20 (10–50)	16 (10–46)	<0.001
male	33 (12–65)	30.5 (16–50)	0.05
SPPB			
median (range)	10 (4–12)	10 (0–12)	0.21
very low	0 (0)	3 (5)	
low	7 (7)	4 (7)	
moderate	32 (32)	18 (30)	
high function	61 (61)	36 (59)	
Psychosocial Metrics: median (range) or no. (%)			
Anxiety – HADS			
median (range)	6 (0–18)	5 (0–15)	0.06
none (0–7)	70 (70)	42 (69)	
borderline (8–10)	16 (16)	13 (21)	
case definite (11+)	14 (14)	6 (10)	
Depression - HADS			
median (range)	4 (0–13)	4 (0–12)	0.48
absent (0–7)	81 (81)	54 (89)	
borderline (8–10)	14 (14)	5 (8)	
case definite (11+)	5 (5)	2 (3)	
Social Support MOS			
median (range)	83 (31–95)	87 (33–95)	0.74
Cognition - 3MS			
median (range)	97 (82–100)	98 (90–100)	<0.001

Body Mass Index (BMI) Karnofsky Performance Status (KPS) Brief Fatigue Inventory (BFI) Human Activity Profile (HAP) Maximum Activity Score (MAS) Adjusted Activity Score (AAS) Medical Outcomes Study–Social Support Survey (MOS–SSS) Short Physical Performance Battery (SPPB) Hospital Anxiety and Depression Scale (HADS) Modified–Mini–Mental Status (3MS)

Table 3
Geriatric Assessment Relationship with Length of Stay and Hospital Readmissions (Univariate Associations)

Geriatric Domains Baseline	Metrics	Length of Stay (Days)		Hospital Readmissions	
		Coefficient (95% CI)	P-value	Odds Ratio (95% CI)	P-value
Clinical	Age	-0.01 (-0.11-0.10)	0.92	0.98 (0.91-1.06)	0.63
	KPS 90% vs. <90%	-0.68 (-2.45-1.10)	0.45	0.76 (0.23-2.50)	0.65
	HCT-CI	0.17 (-0.14-0.48)	0.28	1.28 (0.97-1.69)	0.08
Cellular Senescence	p16	-0.29 (-0.70-0.11)	0.16	0.83 (0.43-1.62)	0.58
	p16 (adjusted for age)	-0.27 (-0.69-0.14)	0.20	0.87 (0.45-1.69)	0.68
Fatigue	BFI	0.06 (-0.28-0.40)	0.73	1.08 (0.82-1.43)	0.58
Psychosocial Factors	HADS	0.05 (-0.06-0.16)	0.38	1.10 (1.00-1.22)	
	HADS Anxiety	0.11 (-0.09-0.32)	0.29	1.14 (0.98-1.32)	0.09
	HADS Depression	0.01 (-0.18-0.21)	0.88	1.17 (0.97-1.41)	0.11
	MOS Social Support	-0.03 (-0.08-0.03)	0.33	1.00 (0.96-1.04)	0.81
	3MS	-0.10 (-0.44-0.24)	0.57	0.99 (0.83-1.19)	0.93
	HAP AAS *	-0.65 (-1.15- -0.15)		0.66 (0.45-0.95)	
Function	HAP MAS *	-0.54 (-1.08- -0.01)		0.85 (0.56-1.28)	0.43
	SPPB	-0.52 (-1.03- -0.02)		0.78 (0.59-1.04)	0.09
	Handgrip Strength Dominant **	-0.06 (-0.14-0.03)	0.18	0.90 (0.82-0.98)	
	Handgrip Strength Non-dominant **	-0.05 (-0.13-0.03)	0.25	0.94 (0.86-1.02)	0.15
	Number of Falls	0.07 (-0.62-0.77)	0.84	1.60 (1.07-2.38)	
	Weight Loss	0.77 (-0.85-2.39)	0.35	5.65 (1.17-27.24)	
Nutrition					

* 10 unit increase

** adjusted for gender Kamofsky Performance Status (KPS) Hematopoietic Cell Transplant Co-morbidity Index (HCT-CI) Brief Fatigue Inventory (BFI) Human Activity Profile (HAP) Maximum Activity Score (MAS) Adjusted Activity Score (AAS) Medical Outcomes Study-Social Support Survey (MOS-SSS) Short Physical Performance Battery (SPPB) Hospital Anxiety and Depression Scale (HADS) Modified-Mini-Mental Status (3MS)

Table 4

Geriatric Assessment Relationship with Pre-Transplant p16

Geriatric Domain Baseline	Metric	Spearman Correlation Coefficient p16 ^{INK4a}	P-value
Physical Function	Brief Fatigue Inventory (BFI)	R = 0.28	
	Falls	R = -0.12	p=0.35
	Handgrip Strength		
	Dominant		
	Male	R = 0.02	p=0.93
	Female	R = 0.07	p=0.71
	Non-dominant		
	Male	R = 0.07	p=0.70
	Female	R = -0.09	p=0.61
	Human Activity Profile (HAP)		
Psychological Status	HAP-MAS	R = -0.07	p=0.56
	HAP-AAS	R = -0.04	p=0.76
	Short Physical Performance Battery (SPPB)	R = 0.14	p=0.27
	Karnofsky Performance Status (KPS)	R = 0.01	p=0.95
	Medical Outcomes Survey (MOS-SSS)	R = -0.08	p=0.49
Cognition	Hospital Anxiety Depression (HADS)	R = 0.03	p=0.82
	Modified Mini Mental State (3MS)	R = -0.01	p=0.91