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Undertreatment of Older Patients with Newly Diagnosed Multiple Myeloma in the Era of Novel Therapies

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Abstract

Background—With the expanding armamentarium of therapeutic agents in multiple myeloma (MM), it is important to identify any undertreated patient populations to mitigate outcome disparities.

Methods—We extracted all plasma cell myeloma cases (ICD-O-3 code 9732) in the SEER-Medicare database from 2007–2011. The ICD-O-3 histology code 9732 captures both active MM and smoldering/asymptomatic myeloma. We defined active MM as either having claims indicating receipt of treatments approved for MM or ICD-9 codes for MM defining clinical features, referred to as CRAB criteria. Multivariate logistic regression was performed to determine the variables that were independently associated with receipt of no treatment.

Results—Of the initial 4,187 patients included in the study, 373 patients had no claims indicating receipt of treatments approved for MM and had no ICD-9 codes associated with CRAB criteria, and were excluded from the analyses. Among the 3,814 patients with active MM, 1,445 (38%) did not have any claims confirming that they received systemic treatment. Older age, poor performance indicators, comorbidities, African-American race, and a lower socioeconomic status (SES) including enrollment in Medicaid were statistically significant factors associated with receipt of no systemic treatment.

Conclusions—In this retrospective study of the SEER-Medicare database, we found that age, health status, race, and SES were associated with receiving treatment for MM. These factors have previously been linked to reduced utilization of specific treatments for MM, such as stem cell transplants. To our knowledge, however, this is the first study to show their association with the receipt of any MM therapy.

Keywords

Multiple Myeloma; Elderly; Treatment; Chemotherapy

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Introduction

While advances in multiple myeloma (MM) treatment have improved overall survival, there are disparities in the groups enjoying the benefit of these advances ¹. Historically, older patients have been less likely to receive treatment compared to younger patients ². In addition, studies suggest inferior treatment and survival outcomes among African-American patients with MM ^{3,4}; however, when treatment is similar, outcomes are similar or even superior among African-American patients ⁴⁻⁸. In addition to age and race, other barriers to treatment include limited health literacy ^{9,10}, financial constraints in patients ¹¹, and professional education gaps resulting in delayed dissemination and implementation of advances in treatment into community practice ¹².

Population level data allow us to examine real-world practice patterns, which may reveal disparities that are not evident in clinical trials and studies of selected populations. For example, a retrospective cohort analysis of patients with a diagnosis of first primary AML in the linked Surveillance, Epidemiology, and End Results (SEER)-Medicare database between 2000 and 2009 showed that 60% of older adults in general practice received no treatment within three months of diagnosis ¹³. In the National Cancer Institute (NCI) Patterns of Care study, which is now over 10 years old, 20–30% of patients with MM received no treatment with chemotherapy or novel agents within the first 12 months after diagnosis ¹⁴.

The expanding armamentarium of therapeutic agents in MM has empowered physicians to choose appropriate treatment options, incorporating consideration of side effect profile, financial burden, and individual patient preferences while enhancing survival outcomes. Given the availability of a broad range of therapeutic options including monoclonal antibodies, immunomodulatory drugs (IMiDs), proteasome inhibitors, histone deacetylase (HDAC) inhibitors, chemotherapeutic agents, and autologous stem cell transplantation ¹⁵, it is essential to identify the untreated and undertreated patient populations based on different patient characteristics, treatment-related morbidity and mortality issues, and healthcare system impediments. In this study we looked primarily at the impact of age on therapy and specifically how age and other factors predict receipt of no MM therapy. The identification of these factors may provide the opportunity to minimize barriers to treatment and thereby benefit a greater number of patients afflicted by this disease.

Materials and Methods

Data Sources

We utilized a retrospective cohort analysis of patients with MM in the linked SEER-Medicare database. The SEER program of the National Cancer Institute (NCI) is a source of epidemiologic data on the incidence and survival rates of cancer in the United States. In the SEER-Medicare interlinked database, the SEER data registry is linked to Medicare enrollment and claims data. At the time this study was conducted, the SEER-Medicare linked database included all Medicare-eligible persons appearing in the SEER database through 2011 and their Medicare claims through 2013. This study was approved by the Human Studies Committee at Washington University School of Medicine.

Patient Selection

Eligible patients were diagnosed with MM between January 1, 2007 and December 31, 2011, over 65 years of age at diagnosis, and had been continuously enrolled in Medicare Part A, B, and D starting the year prior to diagnosis. The ICD-O-3 histology code 9732 (plasma cell myeloma) captures both symptomatic MM and smoldering myeloma (SMM)¹⁶. MM warrants treatment, but SMM can be managed through a wait-and-watch strategy. We defined symptomatic MM as having claims for chemotherapeutic agents effective in MM [bortezomib, cyclophosphamide, doxorubicin, lenalidomide, melphalan, thalidomide, vincristine; unspecified antineoplastic chemotherapy or immunotherapy; or autologous or allogeneic stem cell transplantation] or for ICD-9 codes for MM CRAB criteria within 6 months of diagnosis as previously described¹⁷. The diagnosis and procedural codes for the administration of injectable agents, and generic names of prescription drugs approved by the United States Food and Drug Administration (FDA) for MM indication were used to differentiate patients who received treatment from those who did not. Novel therapies were defined as bortezomib, lenalidomide, or thalidomide within 6 months following the diagnosis of MM. Pomalidomide, carfilzomib, vorinostat, elotuzumab and daratumumab were not considered as they were approved after the study period. Dexamethasone or other corticosteroids were not categorized as treatment because of their broad use in a wide array of diagnoses and hence lack of specificity for their use in determining whether a patient received MM treatment¹⁷. Based on the current NCCN guidelines, radiation therapy is not considered a treatment modality for frontline therapy in MM. As such, steroids, radiation therapy or surgery were not categorized as frontline treatment for this systemic disease.

Study Variables

We investigated the following variables to determine whether they are associated with receipt of no treatment in patients with symptomatic MM:

- Age. Patient's chronologic age at the time of diagnosis.
- Race. For our study, race has been categorized as African-American, Caucasian and other including Asian and Hispanic backgrounds.
- Socioeconomic status (SES). The median annual household income (MHI) at the census tract level of each patient's home residence at time of diagnosis and enrollment in Medicaid were used as surrogates for SES.
- Comorbidities. We used established algorithms to calculate Charlson Comorbidity Index (CCI) score for each patient using claims for the 12 months prior to MM diagnosis^{18,19}.
- Performance Status Indicators. SEER does not encompass objective measurements of performance status, such as Eastern Cooperative Oncology Group (ECOG), or Karnofsky performance status scale. We used Medicare claims to identify factors indicating poor performance status, including, but not limited to, manual wheelchairs and power mobility devices, skilled nursing care, physical therapy and occupational therapy services, speech-language pathology

services, oxygen equipment and accessories that were employed 12 months prior to the diagnosis of MM as previously described²⁰.

Statistical Analysis

All statistical analyses were performed using SAS Enterprise Guide 5.1. Demographic and clinical characteristics were summarized by treatment status (receipt of treatment versus receipt of no treatment). Chi-square test for categorical variables and ANOVA test for continuous variables differentiated the differences between the two treatment groups. Univariate and multivariate logistic regression models were created to determine the variables that were independently associated with (1) receipt of no MM treatment overall and (2) receipt of no novel therapies. A p value of <0.05 was considered to be statistically significant.

Results

Four-thousand one hundred and eighty-seven patients were included in the primary analysis. Of these patients, 373 were considered to have a diagnosis of smoldering/asymptomatic MM due to lack of diagnostic codes for CRAB criteria or treatment, thus were excluded from all the analyses. This left 3,814 patients for the final analysis.

The median age of the cohort at the time of diagnosis was 76 years old (range 65–100). Fifty-one percent of patients were female (1964/3814), 77% were Caucasian (2923/3814), 16% African-American (629/3814), and 7% belonged to other races (262/3814). Twenty-four percent (922/3814) of all patients were found to have at least one poor performance status indicator; 71% (2701/3814) of the cohort had at least one comorbidity based on the CCI, and 33% (1245/3814) were enrolled in Medicaid in addition to Medicare. The characteristics of patient population are summarized in Table 1.

Among patients with symptomatic MM, 1,445 (38%) did not have any claims for systemic treatment. At a median follow up of 26 months, 70% of the study population expired. The median overall survival for patients who received no treatment was 9.6 months (95% CI 8.0–12.0) versus 32.3 months (95% CI 30.3–34.4) for those who received treatment.

Older age increased the odds of receiving no treatment by 7% per year of age [adjusted Odds Ratio (aOR) 1.07 per year of increasing age, 95% confidence intervals (CI) 1.06–1.08]. Patients of African-American descent were 26% more likely to receive no treatment [aOR 1.26, 95% CI 1.03–1.54]. Patients with poor performance status indicators had a 49% higher odds of receiving no treatment [aOR 1.49, 95% CI 1.25–1.77]. Comorbidities were associated with receiving no treatment, with the odds increasing by 17% per 1 point CCI score increase [aOR 1.17, 95% CI 1.12–1.21]. The odds of receiving no treatment was increased by 21% in patients enrolled in Medicaid in addition to Medicare [aOR 1.21, 95% CI 1.02–1.42]. Over time, the odds of receiving no treatment has decreased; for each year increase in the year of diagnosis, the odds of receiving no treatment decreased by 10% [aOR 0.90, 95% CI 0.85–0.94]. MHI, other race, and gender were not associated with treatment receipt status in multivariate analysis. Factors associated with receipt of no treatment are presented in Table 2.

Of patients who had any claim indicating receipt of treatment, the vast majority (93%) received novel therapies. A separate analysis was performed to examine factors associated with receipt of no novel therapies. Older patients were less likely to receive novel therapies; the odds of receiving no novel therapies increased by 7% per year of age (aOR 1.07, 95% CI 1.06–1.08). The odds of not receiving novel therapies were 52% higher in patients with poor performance status indicators (aOR 1.52, 95% CI 1.28–1.81). Comorbidities were associated with not receiving novel therapies, with the odds increasing by 15% per 1 point increase in CCI score (aOR 1.15, 95% CI 1.10–1.19). For each year increase in the year of diagnosis, the odds of receiving no novel therapies decreased by 13% [aOR 0.87, 95% CI 0.83–0.91]. Unlike the analysis of factors associated with receipt of no treatment overall, African-American descent and dual Medicaid-Medicare enrollment were not associated with receipt of no novel therapies in multivariate analysis. Factors associated with receipt of no novel therapies have been summarized in Table 3.

Discussion

Our study demonstrates that a significant portion of patients with MM are not receiving treatment within 6 months of MM diagnosis. Patients who do not receive treatment in that time period had significantly worse outcomes. In 2014, the International Myeloma Working Group (IMWG) added three specific biomarkers to the classic MM defining clinical features, referred to as CRAB criteria [elevated calcium, renal failure, anemia, and bony lytic lesions]. These three biomarkers included clonal bone marrow plasma cells $\geq 60\%$, serum free light chain (FLC) ratio ≥ 100 provided involved FLC level is ≥ 100 mg/L, or more than one focal lesion on MRI. The revised IMWG diagnostic criteria for MM accentuate the necessity for earlier diagnosis and treatment of MM to prevent organ damage and optimize the care for patients with MM ²¹.

In addition, we found that older age, African-American race, poor performance status indicators, comorbidities, and dual Medicaid-Medicare enrollment are independently associated with not receiving treatment.

Despite significant improvement in the survival outcomes of older patients with MM within the past decade, the outcomes of older patients continue to lag behind compared to that of young and fit patients ²². Our study found that age was associated with receipt of no treatment, even after controlling for comorbidities and indicators of poor performance status. Age-related under-treatment of the older population is one likely factor contributing to poorer outcomes in older adults ¹. In the current era, chronologic age should not be the sole measure of aging ²³. The field of geriatric oncology is abandoning traditional patterns of using chronologic age in transitioning to a more modern paradigm of considering physiologic age in approaching therapeutic decision making in clinical practice ²⁴ and determining eligibility for enrollment in clinical trials ^{25,26}.

In a study by International Myeloma Working Group, a frailty score comprising age, functional status (measured by independence in ADL and IADL) and comorbidities was associated with overall survival outcomes and non-hematologic adverse events, regardless of International Staging System (ISS) stage, chromosome abnormalities, and therapeutic

options²⁷. The frailty score was associated with greater risk of treatment-related toxicity. Interestingly, these same factors of age, poor performance status indicators and comorbidities were associated with under-treatment in our study, raising the possibility that clinicians had estimated a greater risk of toxicity in these patients, which could have potentially impacted their recommendations to individual patients. There have been clinical trials specifically designed for intermediate-fit and frail patients to help instruct guidelines to personalize therapy in older patients²⁸. The frailty score has the capacity to be utilized in future prospective trials for prognostic purposes. It also can more accurately define the overall fitness of the population, which cannot be captured by age alone. Moreover, patients with MM who score poorly on frailty score are still in urgent need of receiving appropriate therapies and high quality research to determine the suitable treatment strategies for this patient population²⁹. To address this unmet need, the Institute for Advanced Studies in Aging and Geriatric Medicine (IASIA) has called for clinical trials for frail patients with MM to improve evidence-based clinical guidelines to enhance the outcomes of older patients³⁰.

In our study, African-American race was associated with receipt of no treatment overall, but was not a statistically significant factor in receipt of novel therapies. In a SEER-based study by Costa et al, the relative survival rates (RSR) were measured among three major race groups (non-Hispanic-whites, non-Hispanic-blacks and Hispanics) in patients with MM since the era of targeted therapies began. The 10-year RSR showed improvement in all race groups except non-Hispanic Blacks. These results point to a continued racial disparity affecting survival outcomes¹.

In another analysis of the SEER-Medicare database by our group, the patterns of autologous stem cell transplantation and bortezomib use among patients with MM were reviewed between 2003 and 2011. We found that African-American patients were 37% ($P<0.0001$) less likely to undergo stem cell transplantation and 21% ($P<0.0001$) less likely to be treated with bortezomib⁴. These results further highlight the existing racial disparities affecting MM outcomes. Our current study, however, revealed that African-American race was not associated with receipt of novel therapies. An additional study by our group studying the MM cases from 2007–2013 in the SEER-Medicare revealed African-American race was not associated with reduced utilization of lenalidomide for first-line treatment of MM³¹. Given the fact that the data in our current study has been collected between 2007 and 2011, it is possible that, in the course of time, novel agents have become more accessible to African-American patients compared to the earlier days of novel therapies.

Our results disclosed dual Medicare-Medicaid enrollment was associated with receipt of no treatment overall, but not associated with receipt of no novel therapies. Another SEER-Medicare study examined the association between low-income subsidy (LIS) receipt and use of oral immunomodulatory drugs (IMiDs), delays between IMiD refills, and certain outcomes among Part D beneficiaries with MM. The odds of receiving IMiDs was 32% higher in LIS-recipients between the age of 75 and 84 years compared to LIS non-recipients (95% CI 16–47). The LIS receipt significantly lowered refill delays in all age groups (adjusted relative risk, 0.54; 95% CI 0.32–0.92). In addition, LIS recipients had fewer emergency department visits and hospital admissions compared to LIS non-recipients³².

These results point toward barriers to access and affordability as a potential cause of outcome disparities in patients with MM.

We acknowledge that in a subset of older and frail patients, the risks of treatments approved for MM may outweigh the benefits or may not be in line with the individual's goals of care. While this study focuses on effective front-line treatment modalities included in the National Comprehensive Cancer Network (NCCN) guidelines³³, many patients whose treatment was categorized as "no treatment" in this study may have received supportive care including, corticosteroids, bisphosphonates for hypercalcemia and skeletal lesions, radiation therapy for skeletal lesions, intravenous gamma globulin for prevention of infections, and plasmapheresis for hyperviscosity syndrome³⁴. In this study, poor performance status indicators and comorbidities increased the odds of receiving no treatment [aOR 1.49 (95% CI 1.25–1.77) and aOR 1.17 (95% CI 1.12–1.21), respectively]. These patients are more likely to opt for supportive care and potentially hospice enrollment, though this outcome was beyond the scope of the present study. Appropriate hospice enrollment is widely validated as an indicator of quality end-of-life care. A recent study showed that hospice enrollments among patients with MM is increasing over time. A retrospective analysis using the SEER-Medicare database of patients ≥ 65 years of age who had a primary diagnosis of MM between 2000 and 2013, showed a significant increase in hospice use over time, increasing from 28.6% in 2000 to 56.4% by 2013, $p < 0.001$, but no significant increase in late enrollment – defined as stays of ≤ 3 days before death (12% in 2000 to 16.7% in 2013, $p = 0.38$).³⁵ Distinct characteristics of MM compared to other hematologic malignancies, such as incurability and intractable pain related to bone lesions toward the end of life, make hospice an integral part of care for frail patients with MM in whom the risk of standard of care treatment options offsets the benefits.

There are several limitations to this study. While the SEER-Medicare linked database provides a large sample size with diverse demographics, using claims data and ICD-9 codes for their equivalent CRAB criteria to differentiate SMM versus symptomatic MM has inherent deficiencies. It is possible that ICD-9 codes were under- or over-reported due to miscoding in the claims data. There is also a possibility of having missed treatments received by patients in our claims analysis. While the sensitivity and specificity of Medicare claims for MM treatment have not been reported, prior work has shown that Medicare claims were 93% (95% CI 88–96) sensitive for receipt of parenteral chemotherapy³⁶ and 47% (95% CI 32–62) sensitive for receipt of oral chemotherapy³⁷.

Another limitation of our study is lack of data on the reason for receipt of no treatment. We are unable to determine how patient preference, physician recommendation or other contributing factors influenced the decision not to pursue myeloma treatment. Patient preference related to toxicity of treatment may play a significant role. In a study by Postmus et al. treatment benefits (manifested by survival outcomes) and treatment risks (identified as toxicities associated with each treatment) were quantified to help recognize the factors that inform patients' decision in choosing a certain treatment option for MM. This study revealed that survival outcomes were of more vital importance than treatment tolerability when patients select a treatment strategy³⁸. The SEER-Medicare database does not permit study of these factors as a potential contributor to disparities in treatment.

One more limitation of this study originates from the unavailability of prognostic markers such as staging, cytogenetics and molecular features in the SEER-Medicare database. Although high risk cytogenetics and unfavorable mutations, per se, should not justify lack of treatment, it is possible that some patients with extremely poor prognostic features may elect palliative care alone.

In summary, we identified that age, race, comorbidities, poorer performance status indicators and Medicaid status are associated with receipt of no treatment for MM. These results emphasize the need for a multipronged approach to address outcome disparities in MM. Particular attention to aging-related issues is essential to ensure older and frail patients would benefit from the advances achieved in the field similar to young and healthy patients. Efforts to facilitate clinical trial eligibility for older patients will allow translation of treatment strategies designed for older frail patients to real-world populations. Approaches focused on improving treatment tolerability may further diminish outcome disparities in MM by enabling older and vulnerable older adults to receive effective MM therapy³⁹. This multifaceted approach will also require consideration of racial and socioeconomic barriers to access and affordability of therapeutic options that can contribute to receipt of no treatment. With the growing plethora of treatment options for MM, disease-specific, treatment-specific, and patient-specific characteristics must be taken into account when selecting an individualized treatment strategy. In the era of novel therapies, it is upon the healthcare system and healthcare providers to identify and address any barrier leading to under-treatment and lack of treatment of an individual patient with MM.

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Table 1

Characteristics of the study population.

Variables		N = 3,814 (%)	Receipt of treatment (N = 2,369)	Receipt of no treatment (N = 1,445)
Age [median (range)]		76 (65–100)	75 (65–97)	79 (65–100)
Female		1964 (51%)	1,199 (51%)	765 (53%)
Race	Caucasian	2,923 (77%)	1,861 (80%)	1,062 (73%)
	African-American	629 (16%)	343 (14%)	286 (20%)
	Other races	262 (7%)	165 (7%)	97 (7%)
Poor performance indicators		922 (24%)	423 (18%)	499 (35%)
At least one comorbidity based on CCI		2,701 (71%)	1567 (66%)	1134 (78%)
Enrollment in Medicaid in addition to Medicare		1,245 (33%)	690 (30%)	555 (38%)

CCI, Charlson Comorbidity Index.

Table 2

Factors associated with receipt of no MM treatment

Variables	Univariate Analysis OR (95% Confidence Interval)	Multivariate Analysis aOR (95% Confidence Interval)
Older age (per year)	1.08 (1.07–1.09)	1.07 (1.06–1.08)
African-American descent	1.46 (1.23–1.73)	1.26 (1.03–1.54)
Other race	0.96 (0.74–1.24)	0.95 (0.71–1.27)
Poor performance indicators	2.43 (2.09–2.82)	1.49 (1.25–1.77)
CCI score (per unit)	1.24 (1.20–1.29)	1.17 (1.12–1.21)
Medicaid	1.52 (1.32–1.74)	1.21 (1.02–1.42)
Year of Diagnosis (per year)	0.92 (0.87–0.96)	0.90 (0.85–0.94)
Per every \$10,000 increase in median household income	0.94 (0.91–0.94)	0.98 (0.95–1.01)
Female gender	1.10 (0.96–1.25)	1.01 (0.87–1.17)

OR, odds ratio; aOR, adjusted odds ratio; CCI, Charlson Comorbidity Index.

For race, the white race category was used as the reference level.

Table 3

Factors associated with receipt of no novel therapies

Variables	Univariate Analysis OR (95% Confidence Interval)	Multivariate Analysis aOR (95% Confidence Interval)
Older age (per year)	1.07 (1.06–1.08)	1.07 (1.06–1.08)
African-American descent	1.36 (1.15–1.62)	1.16 (0.95–1.42)
Other race	0.91 (0.70–1.17)	0.90 (0.68–1.20)
Poor performance indicators	2.37 (2.04–2.76)	1.52 (1.28–1.81)
CCI score (per unit)	1.22 (1.18–1.26)	1.15 (1.10–1.19)
Medicaid	1.42 (1.24–1.63)	1.13 (0.96–1.33)
Year of Diagnosis (per year)	0.89 (0.85–0.93)	0.87 (0.83–0.91)
Per every \$10,000 increase in median household income	0.94 (0.91–0.96)	0.97 (0.94–1.00)
Female gender	1.12 (0.98–1.27)	1.03 (0.90–1.19)

OR, odds ratio; aOR, adjusted odds ratio; CCI, Charlson Comorbidity Index.

For race, the white race category was used as the reference level.