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Racial Disparities in the Utilization of Novel Agents for Front-line Treatment of Multiple Myeloma

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Abstract

Background: Treatment with novel agents has become the standard-of-care for newly diagnosed multiple myeloma, but members of racial and ethnic minority groups receive these agents at a lower rate than their peers. Researchers have largely attributed this finding to the higher costs of these drugs in respect to traditional chemotherapies but data supporting this hypothesis are lacking. In this study, we compared the relative bortezomib and lenalidomide utilization in patients with newly diagnosed multiple myeloma, hypothesizing that the disparity between white and African-American patients would be greater for lenalidomide due to its higher overall and out-of-pocket costs.

Methods: We reviewed the utilization patterns of bortezomib and lenalidomide using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database.

Results: Bortezomib utilization was 31% less likely for African-Americans compared to whites. There was no statistically significant difference in lenalidomide utilization when other factors were controlled.

Conclusion: Our findings do not support the hypothesis that higher respective costs are the cause of the racial disparities in novel agent utilization for myeloma treatment. We postulate that travel or logistical issues, structural barriers in the medical system, and preferences and biases among patients and providers may also be involved in the observed treatment disparities.

MICRO ABSTRACT

We reviewed the utilization patterns of bortezomib and lenalidomide using the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. Bortezomib utilization was

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Keywords

Cancer disparities; race; access barriers; SEER-Medicare; multiple myeloma

Introduction

It was once believed that African-American patients with multiple myeloma had more aggressive disease based on inferior survival outcomes at the population level. However, recent studies indicate that undertreatment rather than biology is responsible for the poorer outcomes observed. We recently reported that the utilization of the novel agent bortezomib was 37% lower among African-Americans with myeloma than their white peers [1]. The data suggested that, had African-American patients been treated similar to their white counterparts, there would have been no difference in outcomes. Due to treatment disparities, African-Americans had a 10% increased risk for death.

Lenalidomide, like bortezomib, has become one of the primary treatments for myeloma since its approval in 2007. It appears that, like bortezomib, the administration of lenalidomide throughout the myeloma population has been inequitable. A recent study reported that only 19% of African-American patients received lenalidomide during the first year following myeloma diagnosis, compared to 23% of white patients [2].

The increased costs of newer agents is often been cited as a potential cause of treatment disparities among patients with cancer who identify as a racial/ethnic minority. Higher drug costs result in a greater financial burden on patients, often leading them to lower the dosage and frequency of drugs below the recommended level, and avoid filling prescriptions to reduce medical costs, or choosing alternative therapies [3-5]. As African-Americans with multiple myeloma are more likely to have lower socioeconomic status than their white peers [1, 6], it is believed that they may be more sensitive to the higher costs. However, data directly supporting the hypothesized association between higher costs and racial disparities are lacking.

Compared to bortezomib, lenalidomide has been associated with a 5% increase in total health care spending and nearly a 20% increase in out-of-pocket spending [7]. Therefore, we hypothesized that racial disparities in the utilization of lenalidomide would be greater than bortezomib. To test this hypothesis, we compared the relative utilization of bortezomib and lenalidomide among patients with newly diagnosed multiple myeloma.

Methods

For this analysis, we used the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database, which has been described in detail

elsewhere [8]. At the time this study was conducted, the SEER-Medicare linkage included all Medicare-eligible persons appearing in the SEER data through 2013 and their Medicare claims through 2014. This analysis was limited to patients diagnosed between 2007 and 2013, as 2007 is the first year that prescription data is available in the dataset; 2007 also coincidentally coincides with lenalidomide's FDA approval.

In total, 29,245 patients with myeloma were available in the SEER-Medicare database. We excluded cases with duplicate or incomplete records including those diagnosed with myeloma prior to age 65, death certificate or autopsy cases, cases not enrolled in Medicare Part A (inpatient), Part B (outpatient), and Part D (prescription) at diagnosis. In addition, Managed care (HMO) enrollees were excluded as claims for those patients are not included in the dataset. We also excluded all cases that did not have 1 claim within one year prior to diagnosis, as this is another indicator of an incomplete record. Further, cases of suspected smoldering/asymptomatic myeloma were excluded using a previously published algorithm including claims for myeloma diagnostic criteria, commonly referred to as "CRAB criteria" and treatment [9]. This left 6,272 cases available for the analysis.

First-line treatment was defined as any treatment occurring within the first 6 months following myeloma diagnosis. The corresponding HCPCS procedure codes were used to determine bortezomib utilization (C9207, J9041, S0115) and costs from the Part A and Part B claims. Lenalidomide utilization and costs were identified by generic name in the Part D files. The analyses of bortezomib and lenalidomide were independent; patients receiving both agents were indicated as such.

Following standard descriptive and bivariate analyses, multivariate logistic regression models of lenalidomide and bortezomib utilization were created to determine each's drugs utilization among the African-American population controlling for age, gender, year of diagnosis, and previously established proxies for comorbidities and performances status [10, 11].

Results

A total of 6,272 patients met the eligibility criteria for analysis. The median age at myeloma diagnosis was 76 (range 65-100) and 50% were male. Seventy-seven percent were white, 16% were African-American/Black and 6% were another race.

Patient demographics are summarized by race in Table 1. African-Americans tended to be younger and mostly female, while whites were older and mostly male. African-American patients were also much more likely to have coverage from Medicaid, in addition to Medicare, have a higher number of comorbidities, and have a disability suggestive of poor performance status.

The utilization of both bortezomib and lenalidomide were highest among white patients and lowest among African-Americans (Figure 1). In multivariate analysis, African-Americans were 31% less likely to receive bortezomib (aOR 0.69; 95% CI 0.59-0.80; $p < 0.0001$) and members of other races were 21% less likely (aOR 0.79; 95% CI 0.61-0.81; $p = 0.0453$), both compared to whites. However, there was no statistically significant difference in

lenalidomide utilization by race. The results of the full models are detailed in Table 2. The likelihood of receiving either drug decreased with advancing age or with poorer health, and increased in more recent years. Notably, each 1 unit increase in Charlson Comorbidity Index score decreased the odds of lenalidomide utilization by 17% (aOR 0.83; 95% CI 0.80-0.86; $p < 0.0001$); but there was no association between Charlson Comorbidity Index score and bortezomib utilization. Women were slightly less likely to receive bortezomib than men (aOR 0.83; 95% CI 0.75-0.93; $p = 0.0010$); but there was no difference in lenalidomide utilization by gender.

In a post hoc analysis, we included Medicaid enrollment as a proxy for socioeconomic status/poverty. As noted above, Medicaid enrollment was far more common among non-white races. We hypothesized that controlling for Medicaid enrollment would lessen any observed disparity in utilization by race if costs were the primary driver. While Medicaid enrollment reduced the likelihood of both bortezomib (aOR 0.69; 95% CI 0.60-0.78; $p < 0.0001$) and lenalidomide (aOR 0.87; 95% CI 0.75-1.00; $p = 0.0422$) utilization, controlling for it resulted in little change in the models. African-American patients were still less likely to receive bortezomib (aOR 0.76; 95% CI 0.65-0.89; $p = 0.0009$) while there was no statistically significant difference in lenalidomide utilization (aOR 0.93; 95% CI 0.78-1.09; $p = 0.3662$).

Discussion

In this study, we found that overall racial minorities were less likely to receive lenalidomide for first-line treatment of multiple myeloma. This is similar to the recent finding of Aliwadhi and colleagues using the same dataset [2]. However, when patient characteristics: age, gender, and comorbidities were controlled, there was no statistically significant difference. As African-American patients were more likely to have comorbidities, and comorbidities were highly associated with lower odds of lenalidomide utilization, controlling for comorbidities had a mediating effect on the relationship between race and lenalidomide utilization.

Our hypothesis was that the disparities in lenalidomide utilization would be larger than disparities in bortezomib utilization as lenalidomide is associated with higher overall and out-of-pocket costs than bortezomib. While the results did not support this hypothesis, it is important to note that we were not able to actually analyze treatment cost in this study. While Medicare files do include the costs paid for by Medicare and those deemed to be the patient responsibility, i.e. copays, deductibles, unapproved claims, etc, it is not possible to determine how much the patient was actually billed or paid. An estimated 80% of Medicare beneficiaries have some type of supplemental insurance, including Medicaid, [12] that would assume some or all of the costs not covered by Medicare. In addition, patients may receive prescription benefits from their supplemental insurance or receive some other form of copay assistance. These additional sources of funding are not available in the dataset.

In a previous study using the SEER-Medicare dataset, we found that lenalidomide utilization during first-line treatment was associated with \$4,051 increase in overall spending over the first 84 days of treatment compared to bortezomib [13]. Combination therapy with both

lenalidomide and bortezomib, a common regimen in more recent years, was associated with \$23,213 increase in overall spending. However, as noted above we are unable to determine what part of these costs, if any, were actually paid by the patient. This data indicating a higher overall cost with lenalidomide, the previous report of higher out of pocket costs associated with lenalidomide [7], and our personal experience caring for patients with myeloma support our belief that patients experience higher out-of-pocket expenditures with lenalidomide as compared to bortezomib.

Despite, the uncertainty in costs incurred by the patients, our findings suggest that treatment disparities are not solely a result of cost but are more complex. We hypothesize, that logistical concerns of patients (travel, visits), structural barriers in the health care system (referral bias, cultural barriers, a lack of coordination of care, or conscious or unconscious bias among physicians), as well as cultural differences between white and non-white patients (personal preferences or mistrust of the medical system) are all likely involved. This view is consistent with the findings of the Institute of Medicine in the seminal report “Unequal Treatment” which concluded that:

“The sources of these disparities are complex, are rooted in historic and contemporary inequities, and involve many participants at several levels, including health systems, their administrative and bureaucratic processes, utilization managers, healthcare professionals, and patients.” p. 1. [14]

Based on the findings of the current study, we postulate that lenalidomide, and its oral administration, may help overcome treatment barriers that patients with myeloma face. We have previously reported that lenalidomide treatment is associated with about 40% fewer days of interaction with the medical system than bortezomib [13]. For patients with travel issues and those having difficulty navigating the health care system, lenalidomide may seem like the favorable alternative. It is important to note that, although randomized control trials of bortezomib versus lenalidomide are lacking, studies using secondary real-world data suggest outcomes are likely comparable [2, 13].

Lenalidomide’s oral formulation, in addition to being associated with less frequent medical visits, may also just be preferable to some patients over injectable medications. Two recent patient preferences studies reported that patients do consider the mode, frequency, and duration of administration of therapies in their treatment choices [15, 16]. However, in both studies these seemed to be secondary to concerns regarding efficacy and toxicity. In the setting of a choice of lenalidomide versus bortezomib, two fairly well-tolerated and similarly efficacious treatments for first-line myeloma treatment, the oral formulation of lenalidomide may lead some patients to choose it despite its higher cost.

It is also important to note that patient preferences likely evolve over the course of the disease. One study found that patients with multiple myeloma in earlier lines (first or second line) of therapy prioritized tolerability of treatment more than those later in the disease course [15]. The current study only included patients in first-line therapy. It is unclear if the same results would have been observed among patients in later lines.

In addition to patient preferences, consideration must also be given to how internal biases among patients and physicians may also influence treatment choice. Members of the African-American and other minority groups sometimes hold deep-seated fears regarding the medical system. In a study in 2000, Lillie-Blanton et al. found that 30% of Hispanics and 35% of African-Americans believe that racism is a “major problem” in healthcare and over half (58% of Hispanics and 65% of African Americans) were “very or somewhat” concerned that they or a family member would be treated unfairly because of their race/ethnicity [17]. Perhaps patients who have a mistrust of the medical system are more likely to accept an oral treatment over an injectable. Perhaps providers with a conscious or unconscious bias may be more willing to offer an oral treatment over an injectable to an African-American patient. Exploring these hypothetical questions will take qualitative studies with rich data and are beyond the scope of the current study. However, it is important that these possibilities be raised in order to generate discussion among academics, clinicians, and members of the non-medical community.

There are several limitations to this study. First, as noted above, the comparison of cost actually paid by patients for each treatment cannot be measured in the dataset. Secondly, racial and ethnic minorities are underrepresented. Because of this, the comparisons made in this study were largely between white and African-American patients. Although we did include patients of other races, the relatively small sample sizes in each required us to collapse all these patients into one category for the analyses. There is likely much heterogeneity among the members of the “other” group. Thirdly, with claims-based data, it is possible for over- or under-coding of myeloma treatments to skew the results. Because of these limitations, the study findings should be viewed with caution and used to stimulate further exploration of this phenomenon rather than drawing conclusions.

In summary, among patients with myeloma, disparities in novel agent administration do not seem to be explained by higher costs. We hypothesize that logistical concerns of patients, structural barriers in the health care system, and cultural differences between white and non-white patients are all likely also involved. This study highlights the complexity of health disparities and generates additional questions worth exploring.

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Clinical Practice Points

- Patients identifying as racial minorities have lower utilization of lenalidomide and bortezomib for first-line treatment of multiple myeloma.
- This relationship does not appear to be based on the cost of the treatments; the decrease in lenalidomide utilization appears to be related to differences in baseline health status.
- We postulate that travel or logistical issues, structural barriers in the medical system, and preferences and biases among patients and providers may also be involved in the observed treatment disparities.

Figure 1- Utilization Patterns of Novel Agents for First-line Myeloma Treatment

Utilization of novel agents of bortezomib and lenalidomide was highest among white patients and lowest among African-American/Black patients ($p < 0.0001$).

Table 1-

Demographics

	<u>Whites (n=4,855)</u>		<u>Blacks (n=1,021)</u>		<u>Other (n=396)</u>		
Continuous Variables	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>M</i>	<i>SD</i>	<i>p</i>
Age	77.0	7.1	75.4	7.1	76.9	7.2	<0.0001
Comorbidity Index	1.9	1.9	2.7	2.2	2.0	2.0	<0.0001
Categorical Variables	<i>%</i>		<i>%</i>		<i>%</i>		<i>p</i>
Sex							
Male	53		40		45		<0.0001
Female	47		60		55		
Medicaid Beneficiary							
Yes	22		57		64		<0.0001
No	78		43		36		
Performance Status							
Normal	79		69		82		<0.0001
Poor	21		31		18		

Table 2-**Multivariate Results**

Lenalidomide Utilization			
	aOR	95% CI	P
Age (per year)	0.95	0.94-0.96	<0.0001
Year of Diagnosis (per year)	1.24	1.20-1.27	<0.0001
Female Gender	0.99	0.88-1.11	0.8153
African-American Race	0.89	0.75-1.05	0.1582
Other Race	0.89	0.69-1.13	0.3267
Poor Performance Status Indicators	0.83	0.71-0.98	0.0259
Charlson Comorbidity Index Score (per point)	0.83	0.80-0.86	<0.0001
Bortezomib Utilization			
Age (per year)	0.94	0.94-0.95	<0.0001
Year of Diagnosis (per year)	1.29	1.25-1.33	<0.0001
Female Gender	0.83	0.75-0.93	0.0010
African-American Race	0.69	0.59-0.80	<0.0001
Other Race	0.79	0.63-0.99	0.0453
Poor Performance Status Indicators	0.70	0.61-0.81	<0.0001
Charlson Comorbidity Index Score (per point)	0.97	0.94-1.00	0.0373