Prescription Drug Coverage and Outcomes of Myeloma Therapy Among Medicare Beneficiaries

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ABSTRACT

Purpose

Novel parenteral (bortezomib) and oral (lenalidomide) therapies have improved survival in myeloma, but the standard Medicare benefit covers only parenteral drugs. We examined the association between prescription drug coverage, receipt of therapy, and survival among Medicare beneficiaries with myeloma.

Methods

Using SEER-Medicare data, we identified enrollment in a Medicare Part D plan (PDP) or other creditable prescription drug coverage (OCC) among 9,755 beneficiaries who were diagnosed with myeloma in 2006 to 2011. We examined the receipt of active myeloma therapy and that of classic cytotoxic agents or bortezomib as first-line regimen and overall survival. We report relative risk (RR) for binary outcome comparisons and 3-year restricted mean survival time (RMST) ratios, with 95% CI, adjusting for baseline patient- and disease-related characteristics. Beneficiaries with diffuse large B-cell lymphoma, a cancer that is uniformly treated with parenteral chemotherapy, served as a comparison cohort.

Results

Compared with beneficiaries without prescription drug coverage, PDP or OCC enrollees were more likely to receive active myeloma care, and PDP enrollees were less frequently treated with parenteral agents (adjusted RR, 0.86; 95% CI, 0.80 to 0.93) or classic cytotoxic agents in particular (RR, 0.62; 95% CI, 0.51 to 0.76). Overall survival was significantly better for beneficiaries with PDP coverage (adjusted RMST ratio, 1.16; 95% CI, 1.11 to 1.20) or OCC (RMST ratio, 1.16; 95% CI, 1.12 to 1.21). In contrast, we observed no survival differences by prescription drug coverage status in the control cohort with lymphoma.

Conclusion

Prescription drug coverage is associated with decreased use of classic cytotoxic chemotherapy and better survival among Medicare beneficiaries with myeloma, which suggests improved access to all existing treatment options. As oral targeted agents increasingly replace parenteral chemotherapy in oncology, adjustments in coverage policy are needed to ensure access to optimal treatment.

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INTRODUCTION

The role of orally administered agents in oncology has been steadily increasing. In plasma cell myeloma, therapy was revolutionized in the mid-2000s by the emergence of two novel classes of drugs.¹ Bortezomib is a parenterally injected proteasome inhibitor approved by the US Food and Drug Administration in 2003 for myeloma. Two immunomodulatory drugs (IMiDs)—thalidomide and lenalidomide—are orally administered and approved in 2006. Before these approvals, most older patients with myeloma were treated using corticosteroids, alkylating agents, or

parenteral cytotoxic chemotherapy, such as vincristine, doxorubicin, and dexamethasone, which were relatively inexpensive but provided median overall survival (OS) of only 3 years.^{2,3} Bortezomib or IMiDs improved median survival to 4 to 5 years, and whereas a differential advantage of bortezomib- or IMiD-based regimens has not been demonstrated, their concurrent use further improves survival.⁴⁻⁷ Both agents are substantially more expensive than classic therapies, which creates a financial barrier for Medicare beneficiaries, who constitute a majority of patients with myeloma in the United States.⁸ Whereas the traditional Medicare Part B covers most parenteral chemotherapy costs, including bortezomib, it does not

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pay for most prescription drugs, including IMiDs (Table 1). Supplemental medical coverage increases the likelihood of receiving anticancer therapy in general, yet Medicare beneficiaries had a notably lower uptake of bortezomib and IMiDs compared with patients with other types of health insurance.^{9,10}

In 2006, just at the time of the US Food and Drug Administration approval for IMiDs, Medicare implemented the Part D prescription drug benefit, which provided a new form of coverage for orally administered medications through Part D plans (PDPs) offered as either stand-alone plans or as part of comprehensive managed-care—Medicare Advantage—health coverage.¹¹ For Medicare fee-for-service beneficiaries, PDP enrollment is voluntary and requires monthly premiums. Participation in the Part D program increased from 52% in 2006 to 71% in 2016.¹² Alternatively, beneficiaries may obtain prescription coverage through employer-sponsored plans or Federal Employee or Veterans' Benefits, which are collectively referred to as other creditable coverage (OCC). Beneficiaries who are dual eligible for Medicaid are automatically enrolled in a PDP with low-income subsidies, which largely limit out-of-pocket costs. Implementation of the Part D benefit has generally improved access to oral drugs, but the association with specific cancer treatments or outcomes is unknown.¹³⁻¹⁵

The differential coverage of oral and parenteral therapies affects Medicare beneficiaries with any cancer. For the treatment of myeloma, patients can receive highly effective parenteral and oral options for an additional survival benefit, which offers an opportunity to examine how the new prescription drug coverage influenced treatment selection and outcomes. Bortezomib-based regimens are covered for all Medicare beneficiaries under Part B. In contrast, beneficiaries without prescription drug coverage face a steep, selective financial barrier to initiating IMiDs, which cost more than \$10,000 per month of therapy. Those with PDP or OCC coverage would have markedly lower out-of-

pocket cost for oral IMiDs, despite a residual barrier related to cost-sharing provisions.^{16,17}

Our objective was to examine the association between prescription drug coverage and the receipt of active care for myeloma, the use of parenteral chemotherapy, and subsequent survival. Having coverage may affect the choice of treatment of myeloma—in addition to supportive care and control of comorbidities—which, in turn, would mediate health outcomes, such as survival (Data Supplement). First-line treatment may have a particular impact, as older Medicare beneficiaries may not receive second-line regimens as a result of functional decline with disease progression. We hypothesized that having prescription drug coverage would be associated with an increased receipt of active myeloma care, less use of classic cytotoxic agents, and better survival. We further hypothesized that the relationship between prescription drug coverage and survival would not be observed in diffuse large B-cell lymphoma (DLBCL), a cancer that is uniformly treated with parenteral chemotherapy.

METHODS

Data Source and Study Population

The current study was approved by the institutional review board at Rhode Island Hospital. The SEER-Medicare data set contains cancer registry records of Medicare beneficiaries from 13 geographic areas inhabited by 28% of the US population, linked to administrative claims for all covered inpatient (Part A) and outpatient (Part B) health services.¹⁸ We selected patients with myeloma (Fig 1) who had a histologically confirmed diagnosis in 2006 to 2011 and complete Part A/B Medicare claims from 1 year before diagnosis until December 2013. Medicare Advantage, or managed care, plan enrollees were excluded as their claims were not available.

Table 1. Characteristics of Prescription Drug Coverage Options Available to Fee-for-Service Medicare Beneficiaries and Typical Out-of-Pocket Liability for Bortezomib or Oral IMiDs

Description		Type of Prescription Drug Coverage			
		No Coverage	PDP	OCC*	Medicaid
Coverage characteristic	Beneficiary is responsible for all prescription drug costs	Privately managed prescription plans are available to all Medicare beneficiaries	Provided by employer, Federal, military, or veterans' benefits	Available to qualifying low-income beneficiaries at minimal or no cost	
	Charity financial assistance—outside Medicare—is available for some drugs	Beneficiary must voluntarily enroll and pay monthly premiums	Coverage must meet minimum criteria equivalent to PDPs according to law	Qualifying beneficiaries enroll automatically in a plan with low-income subsidy	
		Enrollment allowed only at initial Medicare enrollment or in specified open enrollment periods	Coverage varies, often more generous than PDPs	Participants may switch plans or unenroll at any time	
		Includes complex coinsurance cost-sharing provisions		Most cost-sharing provisions of traditional PDPs are eliminated	
Out-of-pocket liability					
Parenteral agents (including bortezomib), %	0-20 (depending on medical supplement)†	0-20 (depending on medical supplement)†	< 20 (medical supplement typically provided)†	0	
Oral agents (including IMiDs), %	100	< \$3,000 for initial fill; 5% in catastrophic phase	Varies by plan; out-of-pocket liability is often capped	Minimal (median, \$6)	

Abbreviations: OCC, other creditable coverage; IMiD, immunomodulatory drug; PDP, Part D plan.

*Including retiree health plans, Federal Employee Health Benefits, and military or veterans' benefits.

†Approximately 80% of beneficiaries have a supplementary medical plan that covers most of the Part B medical liability.

Fig 1. CONSORT diagram of cohort selection criteria. PDP, Part D plan.

Variables and End Points

Patients were classified according to prescription drug coverage at the time of myeloma diagnosis. Medicare files reflect coverage by PDP, OCC, or dual Medicare/Medicaid. The reference category consisted of beneficiaries without any prescription drug coverage. Medicare/Medicaid dual enrollees were a distinct category because of minimal cost-sharing requirements, known higher prevalence of comorbidities and disability, greater health care resource use, and worse survival.^{17,19} To examine potential changes in prescription drug coverage after myeloma diagnosis, we additionally identified beneficiaries' coverage status in January of the subsequent calendar year, after the next open PDP enrollment period.

We studied associations between the exposure—prescription drug coverage status—and OS, the main outcome of interest. Among patients who received active myeloma care, we further studied the receipt of classic cytotoxic agents or bortezomib as the first-line regimen. Use of oral agents could be identified only among PDP enrollees, so we could not examine the use of IMiDs or chemotherapy in general. The indicator of active myeloma care (described in detail in the Data Supplement) was defined as two or more outpatient physician visits or receipt of parenteral chemotherapy. Among PDP enrollees, the indicator captured > 98% of patients receiving any chemotherapy, including IMiDs. Following the practice from prior SEER-Medicare studies, we identified first-line chemotherapy that was initiated within 12 months from diagnosis and assigned regimens on the basis of the drugs administered during the first 60 days of treatment.^{10,17} Parenteral drugs were identified by specific Healthcare Common Procedure Coding System codes or were assumed when inpatient chemotherapy was administered—as is typical for vincristine, doxorubicin, and dexamethasone.²⁰⁻²² Intravenous vincristine, doxorubicin, cyclophosphamide, carmustine, and inpatient chemotherapy were designated as classical cytotoxic agents. Survival was calculated from myeloma diagnosis until death or administrative censoring on December 31, 2013. Among PDP enrollees, we described the use of IMiDs and bortezomib in detail on the basis of Part D claims, which were available from January 2007 through December 2013.

Medicare claims do not contain laboratory results or direct clinical assessments; therefore, for adjustment in multivariable regression models, we used claims-based proxies for myeloma severity and baseline health.

These included the Klabunde-Charlson comorbidity index,²³ which correlates with mortality, and Davidoff's disability indicator,²⁴ a validated measure of self-reported performance status.²⁵ Using Medicare claims from 1 year before myeloma diagnosis, we further identified clinically relevant diagnoses and services: hospitalizations, preexisting monoclonal paraproteinemia, anemia, neuropathy, or kidney disease.²¹ To maximize the specificity of indicators, corresponding diagnosis or Healthcare Common Procedure Coding System codes had to occur either in inpatient claims or at least twice and ≥ 30 days apart in outpatient claims.²⁶

Comparison Cohort

In our primary analysis, we hypothesized that having outpatient prescription drug coverage would be associated with increased receipt of active myeloma therapy, less use of classic cytotoxic agents, and improved survival as a result of the mediating effect of coverage on access to oral IMiDs. To address the possibility of unobserved confounding, we replicated the analysis in a contemporaneous cohort of beneficiaries with DLBCL, which is uniformly treated with parenteral immunochemotherapy. We hypothesized that the association between prescription drug coverage and survival would be absent in this negative control cohort.

Statistical Analysis

Continuous variables were reported as medians and interquartile ranges, and proportions were tabulated. All regression models included clinically relevant explanatory variables regardless of their statistical significance: age, categorized into 5-year ranges; sex; race; marital status; year of diagnosis; indicators of comorbidities; performance status; hospitalizations; paraproteinemia; anemia; neuropathy; or kidney disease. For binary dependent variables, we used hierarchical multivariable robust Poisson models, which directly model relative risk (RR).²⁷ Geographical variation was accounted for by using state of residence as a random intercept. Because of evident nonproportional hazards, survival was compared using adjusted restricted mean survival time (RMST) ratios, bounded by 3 years of follow-up—with a sensitivity analysis at 1 and 5 years—and calculated from a multivariable flexible parametric model,

additionally adjusting for state of residence.^{28,29} In contrast to the traditional hazard ratio, an RMST ratio > 1 indicates longer—that is, better—mean survival. All models report estimates with 95% CI. All analyses were conducted using SAS (SAS/STAT User's Guide, Version 9.4; SAS Institute, Cary, NC) and STATA software (15.1/MP; STATA, College Station, TX; Computing Resource Center, Santa Monica, CA).

RESULTS

Among 9,755 beneficiaries with myeloma, 15% had no prescription drug coverage at diagnosis, 34% had a PDP coverage (without Medicaid), 37% had OCC, and 14% were Medicaid dual enrollees (Table 2 and Data Supplement). Compared with beneficiaries without coverage, PDP enrollees had more comorbidities, including myeloma-specific complications—anemia, neuropathy, or kidney disease. Beneficiaries with OCC were more often male and married. Medicaid dual enrollees differed from other groups, being more often female, nonwhite, not married, having more comorbidities, and worse performance status. Only 5% of the study population underwent stem-cell transplantation.

The overall proportion of beneficiaries who received active myeloma care increased from 88% in 2006 to 91% in 2011. The proportion who received any parenteral chemotherapy doubled from 24% to 48%, respectively, mainly as a result of the expanding use of bortezomib (Fig 2A). Median time from diagnosis to treatment was 1.3 months (interquartile range, 0.8 to 2.8 months). Among PDP enrollees (Fig 2B), for whom we could observe all parenteral and oral regimens, the proportion who received IMiDs remained fairly steady (31%), whereas the proportion who received bortezomib increased from 13% in 2007 to 44% in 2011. The proportion who received both bortezomib and IMiD increased from 3% to 13%, respectively.

Treatment of myeloma significantly differed according to the type of prescription drug coverage. Adjusting for baseline characteristics and compared with beneficiaries without coverage, PDP enrollees were 6% more likely to receive active care for myeloma, 14% less likely to receive parenteral chemotherapy, and 38% less likely to receive classic cytotoxic agents without significant difference in bortezomib use (Table 3). OCC recipients were 3% more likely to receive active myeloma care, but did not differ from beneficiaries without coverage

Table 2. Characteristics and Outcomes of Patients With Myeloma, Stratified by Prescription Drug Coverage at Diagnosis

Characteristic and Treatment	Prescription Drug Coverage at Diagnosis			
	No Coverage	PDP	OCC	Medicaid Dual Enrollee
Total	1,460	3,283	3,607	1,405
Age, median (IQR)	77 (71.0-83.0)	77 (71.0-82.0)	77 (72.0-82.0)	76 (71.0-82.0)
Sex				
Women	726 (49.7)	1,564 (47.6)	1,253 (34.7)	819 (58.3)
Men	734 (50.3)	1,719 (52.4)	2,354 (65.3)	586 (41.7)
Race				
White	1,224 (83.8)	2,916 (88.8)	2,985 (82.8)	775 (55.2)
Black	195 (13.4)	277 (8.5)	528 (14.6)	440 (31.3)
Other	41 (2.8)	90 (2.7)	94 (2.6)	190 (13.5)
Marital status				
Married	807 (55.3)	1,836 (55.9)	2,278 (63.2)	434 (30.9)
Other	653 (44.7)	1,447 (44.1)	1,329 (36.8)	971 (69.1)
Histology				
Myeloma	1,371 (93.9)	3,089 (94.1)	3,387 (93.9)	1,326 (94.4)
Plasmacytoma	89 (6.1)	194 (5.9)	220 (6.1)	79 (5.6)
Comorbidity index, median (IQR)*	0 (0.0-2.0)	1 (0.0-2.0)	1 (0.0-2.0)	2 (0.0-3.0)
Claims-based indicators*				
Poor performance status	102 (7.0)	224 (6.8)	208 (5.8)	420 (29.9)
Hospitalization	457 (31.3)	1,069 (32.6)	1,089 (30.2)	625 (44.5)
Monoclonal paraproteinemia	87 (6.0)	286 (8.7)	270 (7.5)	111 (7.9)
Anemia	477 (32.7)	1,155 (35.2)	1,155 (32.0)	684 (48.7)
Neuropathy	29 (2.0)	103 (3.1)	109 (3.0)	64 (4.6)
Kidney disease	219 (15.0)	591 (18.0)	571 (15.8)	350 (24.9)
Treatment				
Active care for myeloma				
No	191 (13.1)	226 (6.9)	379 (10.5)	222 (15.8)
Yes	1,269 (86.9)	3,057 (93.1)	3,228 (89.5)	1,183 (84.2)
Parenteral chemotherapy				
No	939 (64.3)	2,136 (65.1)	2,304 (63.9)	1,029 (73.2)
Yes	521 (35.7)	1,147 (34.9)	1,303 (36.1)	376 (26.8)
Classic cytotoxic agents				
No	1,337 (91.6)	3,111 (94.8)	3,327 (92.2)	1,325 (94.3)
Yes	123 (8.4)	172 (5.2)	280 (7.8)	80 (5.7)
Bortezomib				
No	1,082 (74.1)	2,355 (71.7)	2,595 (71.9)	1,122 (79.9)
Yes	378 (25.9)	928 (28.3)	1,012 (28.1)	283 (20.1)

NOTE. Data are given as No. (%), unless otherwise noted.

Abbreviations: OCC, other creditable coverage; IMiD, immunomodulatory drug; IQR, interquartile range; PDP, Part D plan.

*On the basis of Medicare claims within 12 months before diagnosis.

Fig 2. (A and B) Trends in the proportions of Medicare beneficiaries (A) receiving observable types of myeloma therapy in the entire cohort and (B) receipt of specific regimens among Part D enrollees in whom oral agents could be identified. IMiD, immunomodulatory drug.

in the use of parenteral regimens. Medicaid dual enrollees were equally likely to receive active myeloma care, but significantly less likely to receive any form of parenteral chemotherapy.

We observed that beneficiaries actively changed their prescription coverage status after myeloma diagnosis. Among beneficiaries without coverage at diagnosis, 41% obtained either PDP or OCC by the following January. In contrast, PDP enrollees at diagnosis universally maintained their coverage. There were no significant differences in baseline characteristics between patients who did or did not switch coverage, with the exception that those who obtained PDP or OCC were more likely to have no recorded comorbidities (64% v 54%; $P = .001$) and to undergo a stem-cell transplantation (11% v 7%; $P = .015$). Coverage switching was much less common in the control DLBCL cohort, where only 19% of noncovered beneficiaries switched to PDP or OCC (Table 4).

With a median follow-up of 4.9 years, 70% of patients in the study died and only 17% were censored within 3 years from diagnosis. Median survival in the myeloma cohort was 2.3 years (95% CI, 2.2 to 2.4 years), and 3-year OS was 43.1% (95% CI, 42.1% to 44.1%). Estimates varied according to prescription drug coverage status, with OS higher by 10% at 1 year and 6% at 3 years for beneficiaries with PDP or OCC compared with those without coverage (Fig 3A). Adjusting for baseline characteristics in a multivariable model and relative to the group without coverage, survival

was 16% longer in the PDP group (adjusted RMST ratio, 1.16; 95% CI, 1.11 to 1.20) and 16% longer in the OCC group (adjusted RMST ratio, 1.16; 95% CI, 1.12 to 1.21), without a significant difference between OCC and PDP recipients (adjusted RMST ratio, 1.01; 95% CI, 0.98 to 1.03). Medicaid dual enrollees had notably worse OS both in myeloma and DLBCL, which is consistent with their burden of comorbidities and poor performance status; however, after adjusting for their unfavorable baseline characteristics, Medicaid dual enrollees with myeloma had better OS than those without coverage (adjusted RMST ratio, 1.08; 95% CI, 1.03 to 1.13). As expected, survival differences in myeloma emerged mainly during the first year after diagnosis and decreased over time as patients continued to switch their coverage. In contrast, in the control DLBCL cohort (Fig 3B), we found no significant difference between patients with PDP (adjusted RMST ratio, 1.04; 95% CI, 0.98 to 1.09) or OCC (adjusted RMST ratio, 1.05; 95% CI, 1.00 to 1.10) relative to those without prescription drug coverage. Results were stable in sensitivity analyses that varied the RMST boundary (1, 3, or 5 years; Data Supplement).

DISCUSSION

In this analysis of Medicare beneficiaries with myeloma, the receipt of therapy and survival significantly differed according to

Table 3. Multivariable Models for Receipt of Classic Cytotoxic Agents, Active Myeloma Care, Any Parenteral Chemotherapy, or Bortezomib—as Part of Initial Therapy—Among Medicare Beneficiaries With Myeloma

Prescription Drug Coverage	Active Care for Myeloma*	Any Parenteral Chemotherapy†	Classic Cytotoxic Agent†	Bortezomib-Based Regimen†
None	Reference	Reference	Reference	Reference
PDP	1.06 (1.05 to 1.07)	0.86 (0.80 to 0.93)	0.62 (0.51 to 0.76)	0.91 (0.82 to 1.02)
OCC	1.03 (1.01 to 1.04)	0.95 (0.86 to 1.05)	0.94 (0.83 to 1.07)	0.98 (0.87 to 1.09)
Medicaid dual enrollee	1.02 (1.00 to 1.04)	0.78 (0.69 to 0.89)	0.68 (0.56 to 0.83)	0.79 (0.65 to 0.95)

NOTE. Data are given as adjusted relative risk (95% CI). Full multivariable models with specification of adjustment variables (age, sex, race, marital status, histology, comorbidity index, performance status, year of diagnosis, history of hospitalization, monoclonal paraproteinemia, anemia, neuropathy, or kidney disease, and state of residence used as a random intercept factor) are presented in the Data Supplement.

Abbreviations: OCC, other creditable coverage; PDP, Part D plan.

*Among all patients (N = 9,755).

†Among patients receiving active myeloma care (n = 8,737).

Table 4. Proportions of Patients With Myeloma or DLBCL Who Changed Their Prescription Drug Coverage Status Between the Time of Cancer Diagnosis and January of the Subsequent Calendar Year (after the next open Part D enrollment period)

Coverage Next January*	Coverage at Diagnosis					
	Myeloma			DLBCL		
	No Coverage	PDP	OCC	No Coverage	PDP	OCC
No coverage	571 (59)	< 15 (< 1)†	143 (5)	530 (81)	< 10 (< 1)†	99 (5)
PDP	330 (34)	3,431 (99)	159 (6)	71 (11)	2,495 (99)	54 (3)
OCC	68 (7)	< 15 (< 1)†	2,483 (89)	55 (8)	< 10 (< 1)†	1,810 (92)

NOTE. Data are given as No. (%).

Abbreviations: DLBCL, diffuse large B-cell lymphoma; OCC, other creditable coverage; PDP, Part D plan (with or without Medicaid).

*To avoid guarantee-time bias, analysis was restricted to patients who survived until at least January of the next year after diagnosis (n = 7,202 for myeloma; n = 5,128 for DLBCL).

†Exact number suppressed to protect patients' privacy.

prescription drug coverage status. Patients with PDP or OCC more often received active myeloma care compared with those without coverage. PDP enrollees, nearly one third of whom received oral IMiDs, were 14% less likely to be treated with parenteral chemotherapy and 38% less likely to receive classic cytotoxic agents. Among beneficiaries without coverage, 41% actively obtained it after myeloma diagnosis, but their survival was significantly worse compared with the beneficiaries who had coverage at diagnosis. As most patients with myeloma in the United States are covered by Medicare, our results have important implications both for the clinicians who care for these patients and for health care policy that tackles coverage of oral and parenteral anticancer therapy.

Prior studies that examined the effects of Part D implementation found increased spending on drugs and decreased out-of-pocket costs for patients with cancer, but no consistent improvements in population health or efficiency of care^{13,15,30-32}; however, patients with myeloma report high levels of financial distress, and having prescription drug coverage may influence treatment selection when both parenteral and oral treatments are possible.³³ In this study, Part D coverage was associated with a higher likelihood of receiving active myeloma care and less use of parenteral chemotherapy, particularly classic cytotoxic agents. This decrease was not observed among beneficiaries with OCC, which suggests a potential preference for more aggressive multidrug regimens, such as bortezomib plus cyclophosphamide, in that group. Moreover, the high rate of switching to PDP or OCC coverage after myeloma diagnosis implies that the diagnosis was a strong stimulus to purchase prescription drug coverage, even though the specific clinical reasons for changing coverage were not discernible. Of note, PDP enrollees still face high out-of-pocket costs when initiating IMiD therapy—a median out-of-pocket responsibility of \$3,178 for the first fill, though only \$3 for low-income subsidies recipients—and nearly one half of Medicare beneficiaries use charity assistance to pay for novel oral targeted agents.^{17,34}

The survival difference between beneficiaries with or without prescription drug coverage, which was specific to myeloma and absent in DLBCL, requires cautious interpretation as it is confounded by multiple baseline factors and mediated by the quality of cancer treatment. In observational studies, survival improvements in myeloma have been linked to the use of bortezomib and IMiDs, and we assumed that treatment mediates the association between

prescription drug coverage and survival.³⁵⁻³⁸ In the Mayo clinic experience (2001 to 2010), survival improvement was more pronounced among patients older than 65 years.³⁹ We could not discern whether worse survival in the group without coverage was a result of not receiving therapy at all, an inability to access IMiDs, or poor control of other medical issues. We were also limited by a lack of data on myeloma-specific prognosis, as defined in the Revised International Staging System using serum albumin, β_2 -microglobulin, lactate dehydrogenase, and high-risk cytogenetics⁴⁰; however, patients without prescription drug coverage had fewer comorbidities, which suggests that they may have had less medication needs before their myeloma diagnosis. Early separation of survival curves and the absence of differences in our control DLBCL cohort strongly suggest that patients with myeloma without prescription drug coverage may not have received the most effective first-line therapy. Survival for PDP and OCC groups remained identical, which supports the notion that having any prescription drug coverage contributed to optimal treatment and outcomes.

The primary limitation of this analysis is that unobserved clinical differences between beneficiaries with and without prescription drug coverage could have accounted for the differences in mortality; however, we observed lower prevalence of anemia, kidney disease, and other comorbidities among beneficiaries without coverage compared with the PDP group. Furthermore, use of the negative control DLBCL cohort, which demonstrated no survival differences, supports our findings. Another limitation is that the comparison of treatments was restricted to parenteral regimens, because oral IMiDs were observed to have been administered only for PDP enrollees. The inability to identify oral chemotherapy is a major hurdle for health services research using Medicare data—a problem of increasing importance. Because of this limitation, we could not analyze the receipt of any chemotherapy, and although our indicator of active myeloma care had high sensitivity to detect patients who received oral or parenteral agents, it lacked external validation of its specificity. We were unable to capture the receipt of supplemental medical coverage, which may facilitate access to expensive bortezomib-based regimens, but approximately 80% of PDP enrollees and almost all OCC enrollees have such a supplement.^{9,41} Although the characteristics of individual plans with regard to IMiD coverage were not available, IMiDs are covered by more than 93% of Medicare

Fig 3. (A and B) Overall survival of Medicare beneficiaries with (A) myeloma and (B) diffuse large B-cell lymphoma (DLBCL; control cohort), stratified by type of prescription drug coverage at diagnosis. OCC, other creditable coverage; OS, overall survival.

prescription plans, including OCC.¹⁶ In addition, to account for clinical complications of myeloma—anemia and renal failure—we used claims-based indicators that have been applied in prior literature, but not formally validated. Because of necessary exclusions from the analytic cohort, our findings cannot be extrapolated to Medicare managed-care plan enrollees or to younger patients. Finally, this retrospective analysis does not provide insight into prescribers' behavior or rationale for treatment decisions.

In conclusion, our study demonstrates that, in the setting of myeloma, a cancer that can be treated using highly efficacious oral agents in addition to—or instead of—parenteral chemotherapy, patients with outpatient prescription drug coverage are more likely to receive active care and have longer survival than those without prescription drug coverage. Providing more equitable access to oral and parenteral chemotherapy options may thus enhance outcomes in myeloma and, hypothetically, other cancers that are treatable with oral targeted agents.⁴² Oncologists should identify resources with which to assist their patients in navigating the complex system of Part D coverage rules and plans, thereby helping to optimize the choice and outcomes of therapy. Finally, additional research should clarify the impact of prescription drug coverage on the personal

and societal costs that are associated with expensive novel anti-myeloma treatments, as well as disease-specific and patient-reported outcomes.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Financial support: Adam J. Olszewski
Administrative support: Adam J. Olszewski
Provision of study materials or patients: Adam J. Olszewski
Collection and assembly of data: Adam J. Olszewski
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
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