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ORIGINAL REPORT

Subsidies for Oral Chemotherapy and Use of Immunomodulatory Drugs Among Medicare Beneficiaries With Myeloma

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ABSTRACT

Purpose
The low-income subsidy (LIS) substantially lowers out-of-pocket costs for qualifying Medicare Part D beneficiaries who receive orally administered chemotherapy. We examined the association of LIS with the use of novel oral immunomodulatory drugs (IMiDs; lenalidomide and thalidomide) among beneficiaries with myeloma, who can receive either orally administered or parenteral (bortezomib-based) therapy.

Methods
Using SEER-Medicare data, we identified Part D beneficiaries diagnosed with myeloma in 2007 to 2011. In multivariable models adjusted for sociodemographic and clinical characteristics, we analyzed associations between the LIS and use of IMiD-based therapy, delays between IMiD refills, and select health outcomes during the first year of therapy.

Results
Among 3,038 beneficiaries, 41% received first-line IMiDs. Median out-of-pocket cost for the first IMiD prescription was $3,178 for LIS nonrecipients and $3 for LIS recipients, whereas the respective median costs for the first year of therapy were $5,623 and $6, respectively. Receipt of the LIS was associated with a 32% higher (95% CI, 16% to 47%) probability of receiving IMiDs among beneficiaries age 75 to 84 years and a significantly lower risk of delays between refills in all age groups (adjusted relative risk, 0.54; 95% CI, 0.32 to 0.92). Duration of therapy did not significantly differ between LIS recipients and nonrecipients (median, 7.6 months). Patients treated with IMiDs had significantly fewer emergency department visits and hospitalizations compared with patients receiving bortezomib (without IMiDs), but 1-year overall survival and cumulative Medicare costs were similar.

Conclusion
Medicare beneficiaries with myeloma who do not receive LISs face a substantial financial barrier to accessing orally administered anticancer therapy, warranting urgent attention from policymakers. Limiting out-of-pocket costs for expensive anticancer drugs like the IMiDs may improve access to oral therapy for patients with myeloma.

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INTRODUCTION

Plasma cell myeloma is a bone marrow cancer with median age at diagnosis of 69 years in the United States. Historically, most older patients with myeloma were treated using alkylating agents and corticosteroids, achieving response rates of 40% to 50% and 3-year overall survival rates of 50%.[1-3] Prognosis markedly improved after introduction of two novel classes of agents, the proteasome inhibitors (eg, bortezomib, first approved by the US Food and Drug Administration in 2003) and oral immunomodulatory drugs (IMiDs; thalidomide and lenalidomide, first approved by the US Food and Drug Administration for myeloma in 2006).[4] These drugs are characterized by high efficacy and relatively lower toxicity, increasing response rates to > 70% and 3-year survival to > 65% among older patients.[2-7] By 2007, 75% of newly diagnosed patients in the United States received one of the new agents as part of their initial therapy, whereas the use of traditional chemotherapy decreased.[8] Bortezomib and IMiDs differ in their mode of administration; bortezomib requires twice-weekly parenteral

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injections in the clinic, whereas IMiDs are administered orally. When parenteral and oral options have comparable efficacy, patients with cancer generally prefer orally administered regimens, which avoid painful injections and frequent medical visits.[9] Because bortezomib and IMiDs have not been directly compared in randomized trials, either option (or their combination) is acceptable according to current guidelines for older patients.[10]

The availability of IMiDs coincided with a major change in Medicare coverage for oral anticancer drugs. Medicare has historically paid for parenteral chemotherapy drugs through the Part B benefit (with out-of-pocket costs covered by supplemental insurance for beneficiaries with such coverage). Before 2006, Medicare did not cover outpatient prescriptions, with few exceptions. As a result of the Medicare Modernization Act, in 2006, beneficiaries gained an option to purchase coverage for outpatient prescriptions (including oral anticancer drugs) by enrolling onto privately administered prescription drug plans or comprehensive managed care plans.[11,12] Although this Part D coverage has had a positive impact on access to medications, it requires significant cost sharing by patients who use expensive specialty medications like the IMiDs. In 2017, the out-of-pocket costs include monthly premiums ($15 to $179); a $400 yearly deductible; a 25% coinsurance on the initial $3,700 of gross drug costs; a subsequent coverage gap, which requires $4,950 in out-of-pocket spending; and further 5% coinsurance in the catastrophic phase of coverage.[13]

Previous work has shown that Medicare beneficiaries face high out-of-pocket costs for orally administered anticancer medications and typically meet the threshold for catastrophic coverage with the first prescription.[14] This means that patients who initiate IMiD therapy must pay thousands of dollars in immediate out-of-pocket expenses. Prior studies indicated a relatively lower use of IMiDs and bortezomib among Medicare beneficiaries compared with individuals with private or Medicaid insurance.[8] Part D enrollees also underuse highly effective oral targeted agents in chronic myeloid leukemia.[15,16] Anti-kickback statutes prohibit beneficiaries from receiving direct financial assistance from drug manufacturers in the form of copayment cards or coupons, although charity assistance is allowed. Enrollees with incomes $<$ 150% of the federal poverty level and modest assets are eligible for the low-income subsidies (LISs), which largely eliminate all Part D–related out-of-pocket expenses. LIS recipients include most individuals who are also eligible for state-provided Medicaid assistance (based on poverty), who become automatically eligible for the subsidy. Because of potentially drastic differences in first-line out-of-pocket costs for IMiDs with and without the LIS, we hypothesized that IMiD use, and subsequent outcomes, would differ among Part D enrollees depending on whether they received the LIS.

METHODS

Data Source and Study Population

This research was approved by the Institutional Review Board at Rhode Island Hospital (Providence, RI). From the SEER-Medicare database, we selected patients with myeloma (or plasmacytoma, using the histology codes 9731/3, 9732/3, and 9734/3) diagnosed in 2007 to 2011 (Fig 1). Medicare claims until December 2013 were available. The SEER-Medicare data set provides cancer registry data from 18 geographic areas covering approximately 28% of the US population, linked to complete billing claims for Medicare beneficiaries (93% of records for persons $\geq$ 65 years old).[17] Patients had to be continuously enrolled onto Medicare Parts A and B from 12 months before diagnosis onward, not be participating in a managed care plan (as their billing records would be unavailable), and have Part D coverage at diagnosis. We excluded patients who had prescription coverage provided by other sources (eg, employers, as recorded in Medicare files) or who had no creditable coverage. We additionally excluded patients without histologic confirmation of myeloma, those diagnosed by autopsy, and those who received no chemotherapy within 1 year from diagnosis.

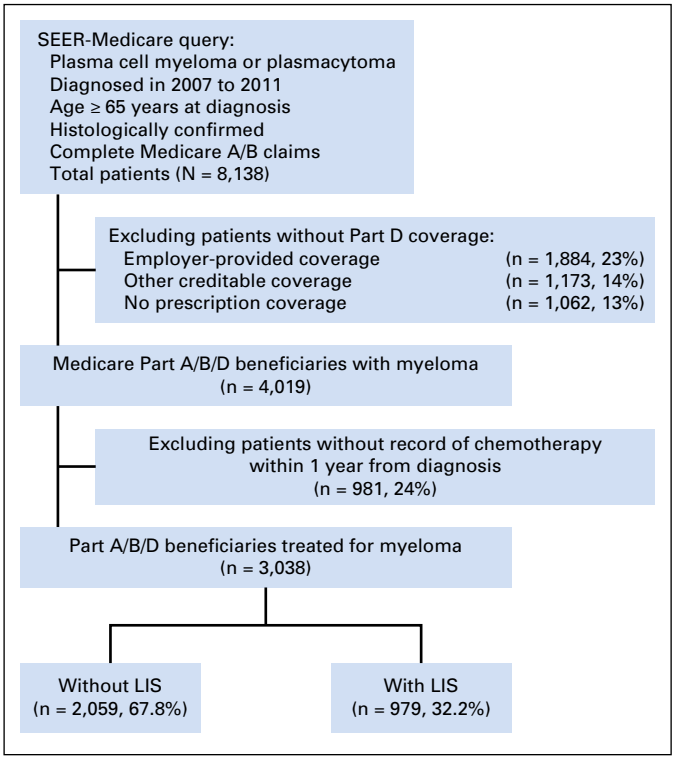

Fig 1. CONSORT diagram. Cohort selection from the SEER-Medicare database. LIS, low-income subsidy.

Measures

Receipt of the LIS was directly recorded by Medicare for every calendar month, and LIS receipt at myeloma diagnosis was the exposure of interest. Use of IMiDs as part of the initial antimyeloma chemotherapy was the primary outcome. We ascertained front-line regimens by identifying drugs administered during the first 60 days of treatment (with a sensitivity check using 30-day and 90-day time frames). Parenteral regimens were identified by outpatient administration of specific drugs.[18,19] Orally administered agents were identified from Part D files. In addition, melphalan and cyclophosphamide, oral alkylating agents covered under Medicare Part B, were ascertained from other Medicare files. For each IMiD prescription, dispensation date, gross drug cost charged by the pharmacy, and dollar amount assigned as out-of-pocket responsibility were recorded. As a measure of adherence to therapy, we analyzed occurrence of a prolonged delay between any two prescriptions for IMiDs, defined as $>$ 45 days from the day the refill was due, during the first 6 months of treatment. Duration of first-line IMiD therapy was defined as time from the first to the last filled prescription.

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Table 1. Characteristics of Patients Stratified by Receipt of LIS

Characteristic	No LIS (n = 2,059)		LIS (n = 979)		*P*
	No. of Patients	%	No. of Patients	%	
Age, years					.76
Median	76		76		
IQR	71-81		71-82		
< 75	942	46	440	45	.22
75-84	867	42	398	41	
≥ 85	250	12	141	14	
Sex					< .001
Women	952	46	585	60	
Men	1,107	54	394	40	
Race					< .001
White	1,878	91	551	56	
Black	121	6	306	31	
Other	60	3	122	13	
Marital status					< .001
Married	1,264	61	309	32	
Other	795	39	670	68	
Poverty prevalence, %*					< .001
< 5	626	30	101	10	
5 to < 10	586	29	166	17	
10 to < 20	543	26	289	30	
≥ 20	280	14	407	42	
Unknown	24	1	16	2	
County of residence*					< .001
Big metropolitan	1,037	50	578	59	
Other metropolitan	632	31	231	24	
Urban/rural	390	19	170	17	
Comorbidity index†					< .001
0	1,061	52	303	31	
1	433	21	241	25	
2	303	15	167	17	
3	136	7	109	11	
≥ 4	126	6	159	16	
Comorbidities of interest†					
Anemia	693	34	466	48	< .001
CKD	348	17	243	25	< .001
Neuropathy	59	3	40	4	.08
Thromboembolism	79	4	48	5	.17
Cardiovascular	408	20	309	32	< .001
Performance status†					< .001
Not poor	1,964	95	747	76	
Poor	95	5	232	24	
Hospitalization†					< .001
No	1,465	71	569	58	
Yes	594	29	410	42	
No. of medical visits†					< .001
0-2	150	7	136	14	
3-6	402	20	202	21	
≥ 7	1,507	73	641	66	
Histology					.21
Myeloma	1,965	95	944	96	
Plasmacytoma	94	5	35	4	
Monoclonal paraprotein†					.80
No	1,888	92	895	91	
Yes	171	8	84	9	
Time from diagnosis to chemotherapy, months					.23
Median	1.1		1.1		
IQR	0.7-1.8		0.7-2.0		
Chemotherapy regimen‡					< .001
IMiD	581	28	276	28	
IMiD + melphalan	61	3	60	6	
IMiD + bortezomib	198	10	74	8	
Bortezomib	533	26	217	22	
Bortezomib + melphalan	78	4	27	3	
Melphalan	124	6	66	7	
Corticosteroids only	371	18	198	20	
Other	113	6	61	6	

(continued on following page)

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Table 1. Characteristics of Patients Stratified by Receipt of LIS (continued)

Characteristic	No LIS (n = 2,059)		LIS (n = 979)		
	No. of Patients	%	No. of Patients	%	*P*
Stem-cell transplantation					
No	1,889	92	950	97	< .001
Yes	170	8	29	3	

Abbreviations: CKD, chronic kidney disease; IMiD, immunomodulatory drug; IQR, interquartile range; LIS, low-income subsidy.
*Poverty prevalence by census tract of residence, county of residence, according to the US Department of Agriculture; big metropolitan: ≥ 250,000 population; other metropolitan: < 250,000 population.
†Based on Medicare claims within 12 months before diagnosis, as detailed in Data Supplement.
‡Other chemotherapy drugs or corticosteroids (when used in combination with chemotherapy) are not included for clarity.

In addition, we evaluated 1-year health outcomes among beneficiaries treated with novel antimyeloma agents, grouped into the following three categories: those receiving first-line bortezomib (without IMiDs), those receiving an IMiD (without bortezomib), or those receiving the combination of bortezomib and IMiD. Outcomes included emergency department (ED) visits, hospitalizations, total Medicare spending, and death. Costs included actual Medicare payments for inpatient, outpatient, and Part D (prescription) services, inflation-adjusted to 2012 dollars using the Consumer Price Index. Costs did not include payments made by patients, supplementary insurance, or other sources.

For adjustments, apart from basic sociodemographic characteristics, we extracted claims-based measures of comorbidity,[20] poor performance status,[21] medical diagnoses corresponding to the toxicity profile of IMiDs, and health services used within the year before myeloma diagnosis (Data Supplement).[19] Prevalence of poverty in the patient's census tract of residence served as an additional indicator of socioeconomic status.

Statistical Analysis

Continuous variables were reported as medians and interquartile range (IQR) and compared using Wilcoxon rank sum test. Proportions were compared using the χ^2 test. Multivariable models were adjusted for all available variables judged to be relevant based on clinical or economic rationale, regardless of statistical significance. For binary outcomes, we used log-linear models with robust SE, which provide direct estimation of relative risk, reported with 95% CIs.[22] Because of a significant interaction between LIS receipt and age, we grouped age into three clinically relevant categories and expressed the main result as marginal semielasticity, accounting for the interaction. Marginal semielasticity indicates, for every age subgroup, the proportional change in the outcome (probability of using an IMiD) for a change in the independent variable (receipt of LIS). Duration of therapy and survival were compared in proportional hazards models, with proportional hazards assumption evaluated using the test by Grambsch and Therneau.[23] Overdispersed count data (ED and hospital visits) were compared using negative binomial models (adjusting for exposure time), and costs were compared using a log-gamma model, without censoring, as all patients had either > 1 year of data or a terminal event.[24] These models included interaction of chemotherapy regimen with LIS receipt, and main results were presented as marginal means with 95% CIs. Regression coefficients for groups were contrasted using Wald tests, without adjustments for multiple comparisons. All analyses were conducted using SAS 9.4 (SAS Institute, Cary, NC) and Stata 14/MP (StataCorp LP, College Station, TX). We used $\alpha < .05$ and two-sided tests of statistical significance.

RESULTS

Patients initiated chemotherapy at a median of 1.1 months (IQR, 0.7 to 1.9 months) from their myeloma diagnosis. Median age was 76 years, 50.6% of patients were women, and 32.2% of patients were receiving the LIS at diagnosis (Table 1). Less than 0.5% of beneficiaries changed their LIS recipient status between the diagnosis and start of treatment. Overall, 1,250 patients (41.1%) received an IMiD as part of their first-line regimen, with lenalidomide gradually replacing thalidomide over time (Data Supplement). In univariable analysis, patients treated with IMiDs were younger, had a better performance status, and had fewer comorbidities, although they had a similar prevalence of plasmacytoma or prior monoclonal gammopathy (Data Supplement).

On average, patients received six IMiD prescriptions during the first year of therapy, at a median gross drug cost of $39,250 (Table 2). Median duration of first-line IMiD therapy was

Table 2. Use of Novel Oral IMiDs With Associated Gross and Out-of-Pocket Costs

Variable	Either IMiD (n = 1,250)	Lenalidomide (n = 769)	Thalidomide (n = 481)
No. of prescriptions (IQR)	6 (2-11)	6 (3-11)	6 (2-11)
Gross drug cost, $			
First prescription, median (IQR)	6,927 (5,125-7,522)	7,351 (6,853-7,700)	5,079 (3,946-6,042)
First year of therapy, median (IQR)	39,250 (15,145-70,133)	45,410 (18,179-82,697)	32,532 (11,777-56,640)
Patient's cost sharing, $			
First prescription			
No LIS, median (IQR)	3,178 (2,079-4,018)	3,552 (2,422-4,138)	2,672 (1,380-3,670)
LIS, median (IQR)	3 (3-6)	3 (3-6)	3 (3-5)
First year of therapy			
No LIS, median (IQR)	5,623 (3,882-9,437)	6,376 (4,131-9,777)	4,847 (3,431-8,318)
LIS, median (IQR)	6 (3-10)	6 (3-9)	6 (3-10)

Abbreviations: IMiD, immunomodulatory drug; IQR, interquartile range; LIS, low-income subsidy.

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Table 3. Multivariable Model for Factors Associated With Use of IMiDs for First-Line Treatment of Myeloma Among Medicare Part D Enrollees Receiving Chemotherapy (N = 3,038)

Variable	Adjusted Relative Risk	95% CI	*P*
Age, years			< .001
LIS nonrecipients			
< 75	Reference		
75-84	0.76	0.68 to 0.85	
≥ 85	0.69	0.57 to 0.84	
LIS recipients			
< 75	1.08	0.94 to 1.23	
75-84	1.05	0.91 to 1.21	
≥ 85	0.67	0.50 to 0.88	
Sex			.12
Female	Reference		
Male	0.93	0.85 to 1.02	
Race			.33
White	Reference		
Black	0.94	0.82 to 1.08	
Asian/other	1.09	0.93 to 1.29	
Marital status			.048
Married	1.10	1.00 to 1.21	
Other	Reference		
County of residence*			.012
Big metropolitan	Reference		
Other metropolitan	1.08	0.98 to 1.19	
Urban/rural	0.89	0.78 to 1.01	
Poverty prevalence, %*			.41
< 5	Reference		
5 to < 10	0.95	0.84 to 1.07	
10 to < 20	1.06	0.94 to 1.20	
≥ 20	1.02	0.89 to 1.17	
Unknown	0.88	0.56 to 1.39	
Permanent disability†	0.87	0.74 to 1.01	.07
Comorbidity index‡			.18
0	Reference		
1	0.88	0.78 to 0.98	
2	0.95	0.81 to 1.11	
3	1.03	0.82 to 1.29	
≥ 4	0.97	0.73 to 1.29	
Poor performance status‡	0.74	0.62 to 0.90	.002
Plasmacytoma histology	0.64	0.48 to 0.84	.002
Monoclonal paraproteinemia‡	0.95	0.81 to 1.12	.57
Hospitalization‡	0.93	0.83 to 1.04	.21
Anemia‡	0.96	0.86 to 1.06	.39
Chronic kidney disease‡	0.76	0.63 to 0.92	.005
Neuropathy‡	1.17	0.94 to 1.47	.16
Thromboembolism‡	0.82	0.63 to 1.06	.12
Cardiovascular disease‡	1.07	0.93 to 1.22	.35
No. of medical visits‡			.010
0-2	Reference		
3-6	1.14	0.95 to 1.36	
≥ 7	1.26	1.07 to 1.49	

Abbreviations: IMiD, immunomodulatory drug; LIS, low-income subsidy.
*Poverty prevalence by census tract of residence, county of residence, according to the US Department of Agriculture; big metropolitan: > 250,000 population; other metropolitan: < 250,000 population.
†Disability indicated as the reason for Medicare enrollment.
‡Based on Medicare claims within 12 months before myeloma diagnosis, as detailed in Data Supplement.

7.6 months, with 38% of patients continuing therapy for > 12 months. Median out-of-pocket expense for the first prescription was $3,178 (IQR, $2,079 to $4,018) for beneficiaries without LIS and $3 (IQR, $3 to $6) for those with LIS. Median out-of-pocket expenses during the first year of therapy were $5,623 (IQR, $3,882 to $9,437) and $6 (IQR, $3 to $10) for those without and with LIS, respectively. Immediately before chemotherapy, 3.9% of all patients were in the catastrophic phase of their coverage, whereas 65.3% reached it with the first IMiD prescription and 79.4% with the second IMiD prescription.

Although the crude proportions of patients receiving IMiDs were similar among beneficiaries with or without LIS (42% and 41%, respectively), LIS recipients had significantly more comorbidities, worse performance status, and less favorable socioeconomic characteristics. Adjusting for those multiple factors, IMiD use was significantly associated with the receipt of LIS (Table 3),

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but the association significantly differed by age group ($P < .001$ for interaction; Fig 2A). LIS recipients age 75 to 84 years had a 32% higher (95% CI, 16% to 47%) relative probability of being treated with an IMiD compared with nonrecipients, whereas the difference was not significant in the younger (semielasticity, 8%; 95% CI, −6% to 21%) and older subgroups (semielasticity, −4%; 95% CI, −37% to 28%). Poor performance status, chronic kidney disease, and plasmacytoma histology were negatively associated with the use of IMiDs.

Among patients treated with IMiDs, the receipt of LIS was associated with a 46% lower probability of a prolonged (> 45 days) delay between any two consecutive IMiD prescriptions (adjusted relative risk, 0.54; 95% CI, 0.32 to 0.92; Table 4), without a significant interaction with age. Duration of IMiD therapy did not significantly differ between LIS recipients and nonrecipients in a multivariable model (adjusted hazard ratio, 1.02; 95% CI, 0.87 to 1.20; Data Supplement).

LIS recipients had a higher incidence of ED visits or hospitalizations and higher costs of care during the first year of treatment (Data Supplement). These outcomes also differed according to type of first-line chemotherapy. Using the group treated with bortezomib as reference, in a multivariable model, patients treated with IMiDs had a significantly lower incidence of ED visits, regardless of the LIS recipient status ($P = .012$ for LIS nonrecipients and $P = .004$ for recipients), whereas the outcome did not significantly differ for the bortezomib plus IMiD combination ($P = .17$ for nonrecipients and $P = .72$ for recipients; Fig 2B). Similarly, in LIS nonrecipients and recipients, hospitalizations were significantly less frequent with an IMiD ($P = .046$ and $P < .001$, respectively) but not with the combination ($P = .54$ and $P = .60$, respectively; Fig 2C). Compared with bortezomib, Medicare spending was similar after first-line IMiD ($P = .06$ and $P = .45$ for nonrecipients and recipients, respectively). It was significantly higher with the IMiD plus bortezomib combination among LIS nonrecipients ($P < .001$), but not among the LIS recipients ($P = .58$; Fig 2D). Compared with patients using bortezomib, those receiving IMiDs had lower costs for inpatient and outpatient medical services, but higher prescription-related Part D spending (Data Supplement). Payments for novel drugs constituted 37% of all spending among beneficiaries receiving bortezomib, 50% among those receiving IMiDs, and 52% among those receiving both. Overall survival at 1 year was 71.4% (95% CI, 68.2% to 74.3%) with bortezomib, 75.1% (95% CI, 72.2% to 77.6%) with IMiDs, and 81.3% (95% CI, 76.1% to 85.4%) with the combination. There was no significant difference between these groups in a multivariable model (Data Supplement).

DISCUSSION

The escalating cost of novel anticancer medications has raised concerns about financial toxicity for patients and health care systems alike.[25-28] Our study is the first, to our knowledge, to

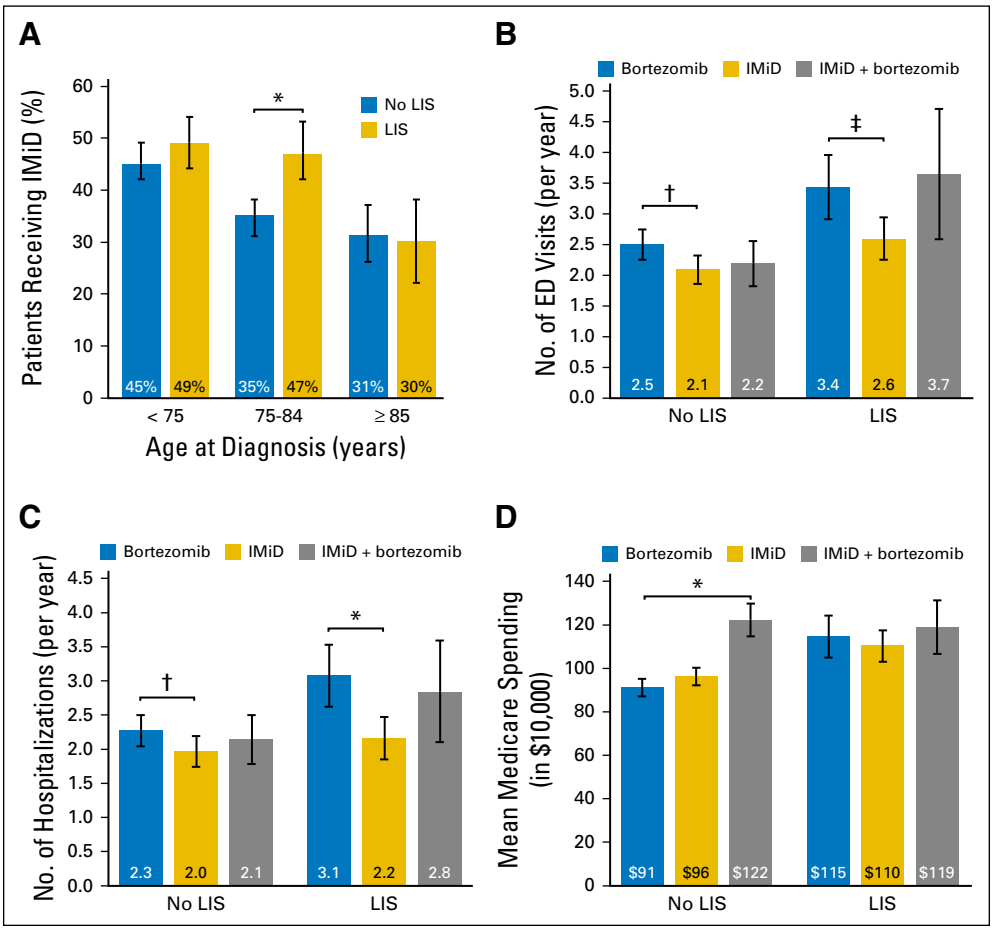

Fig 2. (A) Probability of receiving an immunomodulatory drug (IMiD; lenalidomide or thalidomide), stratified by age group and receipt of the low-income subsidy (LIS). Average incidence of (B) emergency department (ED) visits and (C) hospitalizations during the first year of therapy for myeloma, and (D) cumulative Medicare costs during that year, stratified by type of regimen (bortezomib without IMiD, IMiD without bortezomib, or IMiD and bortezomib) and receipt of the LIS. All estimates are adjusted means derived from multivariable models, with error bars indicating 95% CIs. Horizontal bars with symbols indicate statistically significant contrasts between the groups of interest: (*) $P < .001$, (†) $P < .05$, and (‡) $P < .01$.

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Table 4. Multivariable Model for Prolonged (> 45 days) Delay in Refilling IMiD Prescriptions Among Medicare Part D Enrollees (n = 1,250)

Variable	Adjusted Relative Risk	95% CI	*P*
LIS recipient			.024
No	Reference		
Yes	0.54	0.32 to 0.92	
Age, years			.77
< 75	Reference		
75-84	0.88	0.54 to 1.43	
≥ 85	1.14	0.56 to 2.35	
Sex			.74
Female	Reference		
Male	1.08	0.67 to 1.73	
Race			.058
White	Reference		
Black	2.11	1.12 to 3.98	
Asian/other	1.57	0.70 to 3.51	
Marital status			.38
Married	0.81	0.51 to 1.29	
Other	Reference		
County of residence*			.42
Big metropolitan	Reference		
Other metropolitan	0.72	0.42 to 1.24	
Urban/rural	0.72	0.35 to 1.47	
Poverty prevalence, %*			.002
< 5	Reference		
5 to < 10	0.57	0.29 to 1.12	
10 to < 20	0.93	0.52 to 1.67	
≥ 20	0.87	0.45 to 1.66	
Unknown	5.52	2.00 to 15.28	
Permanent disability†	1.12	0.54 to 2.29	.77
Comorbidity index‡			.017
0	Reference		
1	0.83	0.42 to 1.63	
2	1.18	0.45 to 3.08	
3	1.87	0.56 to 6.30	
≥ 4	4.17	1.34 to 12.97	
Poor performance status‡	0.79	0.28 to 2.24	.66
Plasmacytoma histology	1.68	0.55 to 5.17	.36
Monoclonal paraproteinemia‡	0.80	0.36 to 1.80	.59
Hospitalization‡	1.05	0.60 to 1.85	.85
Anemia‡	1.24	0.71 to 2.18	.45
Chronic kidney disease‡	0.80	0.33 to 1.95	.62
Neuropathy‡	1.26	0.49 to 3.23	.64
Thromboembolism‡	1.02	0.27 to 3.89	.98
Cardiovascular disease‡	0.43	0.21 to 0.88	.022
No. of medical visits‡			
0-2	Reference		.99
3-6	1.04	0.39 to 2.78	
≥ 7	1.03	0.42 to 2.50	
Parenteral chemotherapy	1.64	1.03 to 2.63	.039

Abbreviations: IMiD, immunomodulatory drug; LIS, low-income subsidy.
*Poverty prevalence by census tract of residence, county of residence, according to the US Department of Agriculture; big metropolitan: > 250,000 population; other metropolitan: < 250,000 population.
†Disability indicated as the reason for Medicare enrollment.
‡Based on Medicare claims within 12 months before diagnosis, as detailed in Data Supplement.

examine the association between the LIS, a Medicare policy alleviating patient cost sharing for orally administered chemotherapy, and the use of IMiDs in myeloma—a unique setting where highly efficacious parenteral and oral options became available in the mid-2000s. We found that for Part D beneficiaries without the LIS, the use of IMiDs entailed median out-of-pocket expenses of > $5,600 in the first year, corresponding to 23% of their median yearly income ($24,150 in 2014).[29] These out-of-pocket costs were largely eliminated for LIS recipients, and we found a strong association between the LIS and use of IMiDs among patients age 75 to 84 years. There was also a significant association between the LIS and lower risk of delays in refilling IMiD prescriptions, but not with the overall duration of therapy. Finally, compared with patients treated with bortezomib, those who were treated with an IMiD instead had significantly lower rates of ED visits and hospitalizations but similar costs and survival within a 1-year time frame.

Patients with myeloma report high levels of financial distress.[30,31] The LIS was intended to target financial assistance for the poorest beneficiaries, who are unable to afford Part D–related expenses. However, the resulting 1,000-fold disparity in the out-of-pocket burden for IMiDs between LIS recipients and nonrecipients may result in a differential use of those drugs. Median yearly income of Medicare enrollees decreases with age, from $29,700 for those age < 75 years to $18,850 for those age ≥ 85 years.[29] Our results indicate that patients age 75 to 84 years may be particularly sensitive to financial barriers when choosing their antimyeloma therapy. These findings align with prior studies of associations between cost sharing and use of anticancer treatments. For example, Medicare beneficiaries without supplemental insurance had lower use of cancer chemotherapy overall[32] and of home-based use of erythropoiesis-stimulating agents in myelodysplastic syndrome.[33]

Socioeconomically disadvantaged patients often have lower use of treatments or worse adherence. Conversely, we observed an increased use of IMiDs among LIS recipients with myeloma. Although it is possible that they preferred oral therapy for other reasons, such as inability to travel for injections, association after adjustment for other sociodemographic indicators suggests that the LIS may have facilitated access to IMiDs. This interpretation is corroborated by fewer delays between IMiD prescriptions among LIS recipients, consistent with better adherence to aromatase inhibitors or tyrosine kinase inhibitors in the absence of high out-of-pocket expenses.[15,34] The LIS was not associated with duration of IMiD therapy, suggesting that treatment may have been discontinued because of planned fixed-duration therapy, adverse effects, or poor response, rather than as a result of financial toxicity. Alternatively, extreme high up-front costs may have selected patients with more motivation to continue their therapy, once initiated. The median 7-month duration of therapy seems consistent with contemporaneous clinical trial experience.[2,6,35-37]

The question of potential impact of the policies for oral chemotherapy coverage on health outcomes is complex. Our results suggest that access to IMiDs may be associated with a lower use of ED services and hospitalizations, although short-term survival and Medicare spending did not differ. When IMiDs were used instead of bortezomib, costs were largely shifted from the medical part of the Medicare program onto Part D plans. Even without an overall cost or survival advantage, fewer hospitalizations and ED visits may positively impact patients' quality of life and decrease iatrogenic complications arising from acute care. However, confident assessment of such impact will require further research comparing groups that are more homogeneous with regard to chemotherapy regimens and clinical confounders.

Approaches to mitigate the skyrocketing costs of cancer therapy include value-oriented reimbursement, routine financial

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counseling, and negotiating prices of drugs by Medicare,[25,38-40] but so far, simply deterring patients from treatment by increasing out-of-pocket costs has been commonly applied, despite a conflict with the ethical principle of equality in health care. Some policy observers have expressed concerns that high cost-sharing requirements ration care according to the ability to pay.[41] Many US states have passed parity laws mandating equitable coverage for oral and parenteral anticancer drugs, but the federal Medicare program is exempt from these laws.[42] A more functional solution would require addressing the differential out-of-pocket costs for oral and parenteral chemotherapy in the Medicare program, using input from patients, payers, clinicians, policymakers, and industry.[27,28,31] Meanwhile, shifting from the percentage-based coinsurance to fixed copayments may assure a more predictable out-of-pocket burden, while maintaining patient financial responsibility.

Our analysis had several important limitations. We excluded beneficiaries enrolled onto managed care plans and those with alternative prescription coverage, thus narrowing the scope of the study, but also assuring a more homogeneous population. Individual plans could not be identified, precluding evaluation of plan-specific policies. We could not reliably discern reasons for prescription delays or whether out-of-pocket costs were actually paid by beneficiaries or tertiary sources. Apart from the LIS, some beneficiaries may qualify for financial help from state pharmaceutical assistance programs, although these were not operational in 12 of the 13 states covered by the SEER registries. Comparing out-of-pocket expenses for oral and parenteral chemotherapy would be important to assess true financial toxicity. This was not possible using Medicare data, as patients' responsibility for Part B services was covered to an unknown degree by supplemental insurance held by an estimated 85% of beneficiaries. Our identification of comorbidities through claims may be insufficiently sensitive or specific in relation to actual clinical diagnoses, and we cannot rule out residual influence of additional confounding factors, like the extent or complications of myeloma itself. Finally, further research will need to analyze association of coverage policies with patient-reported or disease-related outcomes, including quality of life and disease-specific survival.

In summary, our analysis suggests that subsidies alleviating patients' financial burden for orally administered chemotherapy may significantly influence treatment selection among certain beneficiaries with myeloma, and their subsequent health outcomes. Policymakers should recognize that the substantial out-of-pocket expenses may compromise access to cancer therapy and lead to catastrophic levels of spending, thereby undermining one of the purposes of health insurance. Although the future direction of the US health care system remains uncertain, coverage for novel oral anticancer agents like the IMiDs warrants reconsideration by Medicare administration to assure equitable access to those treatments for all Americans.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

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Subsidies for Oral Chemotherapy and Use of Immunomodulatory Drugs Among Medicare Beneficiaries With Myeloma

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