Treatment utilization patterns of newly initiated oral anticancer agents in a national sample of Medicare beneficiaries

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What is already known about this subject

- New oral cancer therapies offer greater convenience and fewer side effects, but the responsibility for appropriate administration and monitoring is shifted to patients.
- Medicare patients in particular face unique circumstances that may make adherence a much greater challenge, but most studies that have examined adherence to oral cancer therapies have focused on the commercially insured population.

What this study adds

- This is the first study that offers a wide-ranging assessment of treatment utilization patterns with newly initiated oral anticancer agents across multiple cancers and therapies in a national sample of US Medicare beneficiaries.
- Between 13% and 42% of Medicare patients were nonadherent between the first and last fill of their newly initiated oral anticancer therapies across a range of cancers.
- Our findings provide a valuable benchmark for stakeholders seeking to measure and improve adherence to oral anticancer agents in Medicare patients.

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ABSTRACT

BACKGROUND: Few studies have examined oral anticancer treatment utilization patterns among Medicare beneficiaries.

OBJECTIVE: To assess treatment utilization patterns of newly initiated oral anticancer agents across national samples of Medicare beneficiaries for 5 cancer types: chronic

myeloid leukemia (CML), multiple myeloma (MM), metastatic prostate cancer (mPC), metastatic renal cell carcinoma (mRCC), and metastatic breast cancer (mBC).

METHODS: This retrospective claims analysis used 100% Medicare Chronic Condition Data Warehouse (CCW) Parts A, B, and D files from 2011 to 2014 (for CML, MM, mPC, and mRCC patients) and a 5% random fee-for-service

sample from 2011 to 2013 (for mBC patients). Outcomes of interest were the number of 30-day supply prescriptions, adherence, and discontinuation of newly initiated (ie, index) oral anticancer agents indicated for each of the cancers. Adherence was calculated with both the “traditional” proportion of days covered (PDC) approach, measured over a fixed 1-year period or until hospice/death, and a

“modified” PDC approach, measured over the time between the first and last fill of the index oral anticancer agent. Patients with PDC of at least 0.80 were deemed as being adherent. Discontinuation was defined as the presence of a continuous 90-day gap in the availability of days supply of the index oral anticancer agent.

RESULTS: Our study included 1,650, 7,461, 6,998, 2,553, and 79 patients for CML, MM, mPC, mRCC, and mBC, respectively. Patients with mRCC had the highest proportion of patients with only 1 fill of their index anticancer agent (28%) followed by mBC (17%), MM (17%), mPC (12%), and CML (12%). Patients with CML had the highest mean (SD) number of 30-day supply equivalent prescriptions (8.3 [4.6]), followed by patients with mPC (6.5 [4.2]), MM (5.7 [4.1]), mBC (4.7 [3.2]), and mRCC (4.5 [3.9]). Using the modified PDC measured between the first and last fills, approximately three-quarters of patients with CML (74%), mRCC (71%), and mBC (70%) were adherent to the index oral anticancer agent. Adherence was highest for patients with mPC (87%) and lowest for patients with MM (58%). The percentage of patients defined as adherent to the index oral anticancer agent decreased for all cancers when using the traditional PDC measure over a fixed 1-year period: CML (54%), MM (35%), mPC (48%), mRCC (37%), and mBC (22%). Rates of discontinuation for patients in our sample were 32% (CML), 38% (mPC), 42% (mRCC), 48% (MM), and 58% (mBC).

CONCLUSIONS: Between 13% and 42% of Medicare patients were nonadherent between the first and last fill of their newly initiated oral anticancer therapies across a range of cancers. This study provides a valuable benchmark for stakeholders seeking to measure and improve adherence to oral anticancer agents in Medicare patients.

The past decades have seen an explosion of new oral therapeutic options for cancer patients that may improve survival and outcomes across a wide variety of cancers, including blood cancers, breast cancer, prostate cancer, and kidney cancer. For example, oral tyrosine kinase inhibitors (TKIs) have enabled patients with chronic myeloid leukemia to achieve near-normal life expectancy.^{1,2} In addition to improved outcomes, oral anticancer agents do not require infusion visits and often have better tolerability profiles.³ However, realizing the full benefits of these breakthrough treatments shifts much of the burden for appropriate administration and monitoring from health care professionals to the patient. Hence, a careful examination of adherence to oral anticancer treatments in real-world clinical practice is critical.

The existing literature suggests that measuring adherence among patients receiving oral anticancer agents is a multifaceted problem: rates of adherence vary widely based on adherence assessment methodology, type of cancer and medication, and insurance type.⁴ Medicare patients in particular face unique circumstances such as polypharmacy,

high out-of-pocket costs, and multiple comorbidities that may make adherence a much greater challenge.⁵⁻⁸ While cancer prevalence and incidence are highest among the elderly,⁹⁻¹³ they are often under-represented in cancer clinical trials, and thus adherence to anticancer therapies among Medicare beneficiaries has implications for real-world effectiveness.¹⁴

Despite these facts, most studies have examined adherence within the commercially insured population.¹⁵⁻¹⁷ Previous studies that have examined adherence to oral anticancer agents among Medicare beneficiaries have significant drawbacks.^{18,19} They often use differing measures of adherence, such as proportion of days covered (PDC) or medication possession ratio (MPR), which may either under- or overestimate adherence rates. Further, many studies have only examined adherence for a single cancer or use differing time frames to measure adherence, complicating meaningful comparisons across cancer types. Given these limitations, a broader analysis is warranted.

The objective of this descriptive study was to comprehensively assess treatment utilization patterns of newly initiated oral anticancer agents across national samples of Medicare beneficiaries for the following 5 cancer types: chronic myeloid leukemia (CML), multiple myeloma (MM), metastatic prostate cancer (mPC), metastatic renal cell carcinoma (mRCC), and metastatic breast cancer (mBC).

Methods

DATA SOURCE

This study was performed using the Medicare Chronic Conditions Data Warehouse (CCW) files based on the most recent data available to the authors at the time of the analysis. These files contained data on all fee-for-service (FFS) Medicare beneficiaries, including Medicare Parts A and B medical claims for inpatient care, skilled nursing facility care, home health services, outpatient services, durable medical equipment, and hospice services and Part D prescription claims for outpatient prescription drug events. For patients being treated for CML, MM, mPC, and mRCC, we had access to CCW data for the 100% (ie, national) FFS sample from 2011 to 2014. For patients being treated for mBC, we only had access to CCW data for a 5% random FFS sample from 2011 to 2013.

STUDY DESIGN AND SAMPLE SELECTION

This was a retrospective claims database analysis using Medicare data. Patients were included in the study sampling frame if they had a prescription claim for an oral anticancer drug indicated for CML (bosutinib, dasatinib,

imatinib, nilotinib, ponatinib), MM (lenalidomide, pomalidomide, thalidomide), mPC (abiraterone, enzalutamide), or mRCC (axitinib, pazopanib, sorafenib, sunitinib) between January 1, 2012, and December 31, 2013. For the sample selection of patients receiving oral anticancer treatment for mBC (everolimus, lapatinib), the identification window was between January 1, 2012, and December 31, 2012. Oral anticancer agents approved after December 31, 2012, for mBC and those approved after December 31, 2013, for the remaining cancers were not included given the years of the data available for the study. Of note, this study also did not examine adherence to oral endocrine therapies (eg, tamoxifen) used in breast cancer, as these are older oral therapies wherein there is already extensive adherence literature.

The first claim for the oral anticancer drug was assigned as the index date. Patients were required to have no claims for their index treatment in the 12-month pre-index period to ensure that they were new users of the index anticancer agent. For all cancers of interest, we required patients to have at least 1 claim with a diagnosis for the selected cancer (*International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] codes for CML [205.1], MM [203.0], mPC [185], mRCC [189.0], mBC [174]). In addition, for solid tumor malignancies of mPC, mRCC, and mBC, we required at least 1 claim with a diagnosis for cancer metastases (ICD-9-CM codes: 196, 197, 198, 199) in the 12 months before the index date. We required patients to have continuous FFS Medicare Parts A, B, and D (stand-alone prescription drug plan) eligibility in the 12-month pre-index period and the 12-month post-index period (or until a patient died or entered hospice during the post-index period).

KEY OUTCOME MEASURES

We used multiple measures to assess utilization patterns of the index oral anticancer agent. First, we examined the number of prescription fills for the index oral anticancer agent in the post-index period, overall and stratified by whether the patient died or entered hospice during the post-index period or was still alive at the end of the period. The counts for all prescriptions were standardized into 30-day supply equivalents by dividing the days supply on each prescription claim by 30. This measure provided a conceptually simpler measure of treatment utilization via the number of months a patient had the index cancer drug on hand over the 12-month follow-up. For example, a count of twelve 30-day supply prescriptions indicated that the patient had the whole year with the drug covered. In addition to measuring the mean number of prescriptions filled

over the 12-month follow-up, we also examined the proportion of patients filling only 1 prescription of the index oral anticancer agent.

Next, we examined adherence to the index oral anticancer agent, defined using the proportion of days covered (PDC), measured as the number of days covered with the index oral anticancer agent during a fixed time interval divided by the fixed time interval from date of index treatment initiation. We measured PDC using 2 different definitions for the fixed time interval. Under the first definition, adherence to the index oral anticancer agent was measured between index date and the earlier of 365 days post-index date or until a patient died or entered hospice (“traditional” PDC approach). Under the second definition, adherence to the index oral anticancer agent was measured between the dates of the first fill (ie, index date) and last fill of the index oral anticancer treatment during follow-up (“modified” PDC approach).

The 2 approaches provide a lower bound and upper bound for the adherence estimates. They help with sensitivity analyses to address the key limitation of administrative claims data, wherein we do not know the reasons for the observed refill patterns and whether the individual was truly nonadherent or whether they stopped taking the index anticancer oral agent due to clinical reasons (eg, disease remission, progression, or adverse effects) and/or per the advice of their oncologist.

The traditional PDC approach is more conservative and assumes all patients should have continued their index oral anticancer agent for the 365 days post-index (or at least until they died or entered hospice). The modified PDC approach is more generous and assessed adherence only between the first and last fill of the index oral anticancer agent, permitting the assumption that all patients may have stopped taking the index agent after its last observed fill based on their oncologist's advice. The latter modified PDC approach was also used to allow for differences in how cancer patients utilize oral cancer therapy based on their cancer type. For example, a fixed interval is well suited for CML patients who require lifelong treatment; however, a 12-month interval is not as clinically meaningful for mRCC or mPC, where progression may occur and require a switch in treatment in less than a year. In these instances, the time interval between the first and the last refill date for the index agent may be more appropriate.

Under the modified PDC approach using the first to last fill date as the fixed time interval, we excluded patients who only had a single fill of their index treatment from our adherence calculation. Under both PDC approaches,

patients with a PDC greater than or equal to 0.80 were defined as adherent. In sensitivity analyses, we defined adherence using alternative thresholds as PDC of at least 0.70 and PDC of at least 0.90.

Our third set of outcomes measured discontinuation and persistence. Discontinuation was a dichotomous measure indicating the presence of a 90-consecutive-day period without availability of days supply of the index oral anticancer agent during the 365 days post-index or until a patient died or entered hospice in the post-index period. Among patients who discontinued their oral anticancer agent, we measured the time to discontinuation, defined as the time from the index date to the beginning date of the 90-consecutive-day gap.

For mapping out the measurement of outcomes of adherence, discontinuation, and persistence, we relied on the days supply reported on the prescription claim for the index oral anticancer agent for all except 3 study drugs. The 3 exceptions included 2 of the MM drugs (ie, lenalidomide and pomalidomide) and an mRCC drug (ie, sunitinib). For these drugs, dosing strengths may vary, and patients are on treatment for a defined number of weeks and then off treatment for 1 or 2 weeks. Hence, we manually adjusted the days supply on the prescription based on the quantity of pills reported for the prescription and common dosing regimens. This method of adjusting the days supply of the prescription to better reflect the dosing schedule of the anticancer agent has been used in previously published studies of oral cancer therapy treatment patterns.^{20,21} Additional details on these adjustments to the days supply for lenalidomide, pomalidomide, and sunitinib are available in [Supplementary Table 1](#) (available in online article).

ANALYSIS

Descriptive characteristics such as age, gender, race, region, reason for Medicare eligibility, and National Cancer Institute comorbidity index were generated for each of the cancer populations. Descriptive analyses were conducted to estimate the number of 30-day supply prescriptions, adherence, and discontinuation during the follow-up period. Median time to discontinuation was also estimated. Statistical testing was not conducted because this study was planned as a purely descriptive analysis with no a priori hypotheses. Any estimate based on a cell size less than 11 (or that allowed back-calculation of a cell size to less than 11) was omitted to comply with the Centers for Medicare & Medicaid Services cell size suppression policy.

Results

SAMPLE CHARACTERISTICS

Our study sample selection criteria for identifying new users of oral anticancer agents for the 2 blood cancers resulted in 1,650 patients with CML and 7,461 patients with MM ([Supplementary Table 2](#), available in online article). Similarly, the study samples for new users of oral anticancer agents for the 3 solid tumors included 6,998 patients with mPC, 2,553 patients with mRCC, and 79 (corresponding to a 100% sample of 1,580) patients with mBC. Patient characteristics for these 5 cancer samples are presented in Table 1. The samples were predominantly White (77%-84%). There was a roughly even split between male and female patients for CML and MM, but patients with mRCC were more likely to be male (64%). Additionally, between one quarter and one half of patients qualified for part or full low-income subsidy (Table 1).

NUMBER OF PRESCRIPTION FILLS

Table 2 displays the count of prescription fills for the index oral anticancer agents. We found that the percentage of patients filling only a single prescription varied across cancers (CML=12%; MM=17%; mPC=12%; mRCC=28%; mBC=17%). Patients with CML had the highest mean (SD) number of 30-day supply prescriptions (8.3 [4.6]), followed by patients with mPC (6.5 [4.2]). Patients with MM filled 5.7 (4.1) 30-day supply prescriptions; the fewest prescriptions were filled by patients with mBC (4.7 [3.2]) and mRCC (4.5 [3.9]). Among patients who were alive during the post-index period, the number (SD) of 30-day supply prescriptions was slightly higher for all cancers: 9.0 (4.4) for the CML sample, 8.5 (4.0) for the mPC sample, 6.8 (4.0) for the MM sample, 6.2 (4.4) for the mRCC sample, and 5.6 (3.5) for the mBC sample.

ADHERENCE

Table 3 presents the results of our adherence outcomes using 2 separate definitions of the fixed time interval. Using the traditional PDC measure, the mean (SD) PDC for the index oral anticancer agent was 0.69 (0.32) for patients with CML, 0.69 (0.29) for patients with mPC, 0.61 (0.33) for patients with mRCC, 0.58 (0.31) for patients with MM, and 0.52 (0.29) for patients with mBC. Approximately half of patients with CML (54%) and patients with mPC (48%) were deemed adherent to their index oral anticancer treatment based on a PDC of at least 0.80; a little more than one-third of patients with MM (35%) and mRCC (38%) were adherent. Patients with breast cancer had the lowest adherence rate (22%).

TABLE 1 Sample Characteristics

	Patients who newly initiated an oral anticancer agent indicated for each of the following cancers ^a									
	CML		MM		mPC		mRCC		mBC	
	n	%	n	%	n	%	n	%	n	%
Sample size	1,650	100	7,461	100	6,998	100	2,553	100	79	100
Age, years										
<65	427	26	839	11	342	5	400	16	16	20
65-69	290	18	1,511	20	1,099	16	612	24	25	32
70-74	320	19	1,907	26	1,713	24	660	26	19	24
75-79	265	16	1,516	20	1,551	22	488	19	^b	^b
>79	348	21	1,688	23	2,293	33	393	15	^b	^b
Disability as the original reason for Medicare entitlement	632	38	1,696	23	935	13	689	27	25	32
Sex										
Female	881	53	3,794	51	0	0	930	36	79	100
Male	769	47	3,667	49	6,998	100	1,623	64	0	0
Race										
White	1,348	82	5,764	77	5,731	82	2,137	84	66	84
Black	177	11	1,251	17	809	12	279	11	^b	^b
Latino or other race	125	8	446	6	458	6	137	5	^b	^b
Region										
Northeast	275	17	1,321	18	1,288	18	379	15	12	15
Midwest	420	25	1,830	25	1,661	24	667	26	22	28
West	284	17	1,246	17	1,411	20	443	17	19	24
South	671	41	3,064	41	2,638	38	1,064	42	26	33
Part D LIS status										
Part or Full LIS	723	44	2,371	32	1,885	27	971	38	37	47
Non-LIS	927	56	5,090	68	5,113	73	1,582	62	42	53
Any other oral anticancer treatment in pre-index period ^c	90	5	140	2	50	1	123	5	^b	^b
RxHCC, mean (SD)	3.89 (0.58)	—	2.85 (0.47)	—	1.10 (0.45)	—	1.28 (0.48)	—	0.95 (0.38)	—
Follow-up status										
Hospitalization during follow-up	697	42	4,623	62	3,618	52	1,542	60	39	49
Died or entered hospice during follow-up	210	13	1,973	26	2,941	42	1,216	48	37	47

^aNew users of an oral anticancer agent (ie, index agent) indicated for each cancer (CML: bosutinib, dasatinib, imatinib, nilotinib, ponatinib; MM: lenalidomide, pomalidomide, thalidomide; mPC: abiraterone, enzalutamide; mRCC: axitinib, pazopanib, sorafenib, sunitinib; mBC: everolimus, lapatinib). Oral anticancer agents approved after December 31, 2012, for mBC and those approved after December 31, 2013, for the remaining cancers were not included given the years of the data available for the study.

^bCell sizes with n<11 omitted to comply with the Centers for Medicare & Medicaid Services' cell size suppression policy.

^cAny use of nonindex oral anticancer agent indicated for the specific cancer in the 12-month pre-index period (CML: bosutinib, dasatinib, imatinib, nilotinib, ponatinib; MM: lenalidomide, pomalidomide, thalidomide; mPC: abiraterone, enzalutamide; mRCC: axitinib, pazopanib, sorafenib, sunitinib; mBC: everolimus, lapatinib).

CML=chronic myeloid leukemia; LIS=low-income subsidy; mBC=metastatic breast cancer; MM=multiple myeloma; mPC=metastatic prostate cancer; mRCC=metastatic renal cell carcinoma; NCI=National Cancer Institute; RxHCC=prescription drug hierarchical condition category risk score.

TABLE 2 Number of Prescription Fills for Index Oral Anticancer Agents in the Post-Index Period

Type of cancer and oral anticancer agent	All patients n	Patients with only 1 fill of index oral anticancer agent %	Number of 30-day supply equivalent prescriptions for index oral anticancer agent, mean (SD)		
			All patients	Alive during post-index period	Died or entered hospice during post-index period
CML	1,650	191 (12)	8.3 (4.6)	9.0 (4.4)	3.7 (3.1)
Bosutinib	^a	^a	5.6 (5.9)	5.6 (5.9)	^a
Dasatinib	429	66 (15)	7.8 (4.7)	8.5 (4.5)	3.1 (3.3)
Imatinib	846	82 (10)	8.8 (4.6)	9.5 (4.3)	3.9 (3.1)
Nilotinib	346	38 (11)	8.1 (4.4)	8.7 (4.2)	3.9 (3.2)
Ponatinib	^a	^a	5.8 (2.9)	5.9 (3.1)	5.3 (1.2)
MM	7,461	1,279 (17)	5.7 (4.1)	6.8 (4.0)	2.7 (2.3)
Lenalidomide	6,518	1,065 (16)	5.9 (4.1)	6.9 (4.0)	2.7 (2.3)
Pomalidomide	368	70 (19)	5.5 (3.9)	7.4 (3.7)	3.0 (2.4)
Thalidomide	575	144 (25)	4.4 (3.7)	5.5 (4.0)	2.6 (2.2)
mPC	6,998	871 (12)	6.5 (4.2)	8.5 (4.0)	3.6 (2.6)
Abiraterone	5,585	708 (13)	6.5 (4.2)	8.4 (4.0)	3.7 (2.6)
Enzalutamide	1,413	163 (12)	6.4 (4.2)	8.9 (3.8)	3.6 (2.4)
mRCC	2,553	718 (28)	4.5 (3.9)	6.2 (4.4)	2.6 (2.1)
Axitinib	313	71 (23)	5.3 (4.3)	7.5 (4.5)	3.1 (2.7)
Pazopanib	851	243 (29)	4.7 (4.0)	6.3 (4.4)	2.7 (2.2)
Sorafenib	175	57 (33)	3.8 (3.3)	5.4 (4.1)	2.6 (2.0)
Sunitinib	1,214	347 (28.5)	4.3 (3.8)	5.9 (4.3)	2.4 (1.8)
mBC	79	13 (17)	4.7 (3.2)	5.6 (3.5)	3.6 (2.3)
Lapatinib	^a	^a	4.0 (3.0)	4.6 (3.6)	3.2 (2.0)
Everolimus	^a	^a	5.0 (3.2)	6.0 (3.5)	3.8 (2.4)

^aCell sizes with n < 11 were omitted to comply with the Centers for Medicare & Medicaid Services' cell size suppression policy.

CML = chronic myeloid leukemia; mBC = metastatic breast cancer; MM = multiple myeloma; mPC = metastatic prostate cancer; mRCC = metastatic renal cell carcinoma.

When the modified PDC was measured between first and last prescription fills among those with more than 1 fill of the index oral anticancer treatment as a measure of adherence, the mean (SD) PDC was higher for all cancers: CML (0.85 [0.19]), MM (0.79 [0.20]), mPC (0.92 [0.15]), mRCC (0.85 [0.19]), and mBC (0.86 [0.16]). The percentage of patients defined

as adherent to their index oral anticancer agent based on PDC of at least 0.80 also increased to 74% (CML), 58% (MM), 87% (mPC), 74% (mRCC), and 70% (mBC).

Sensitivity analyses using alternate thresholds for defining adherence showed results as expected. More patients were adherent if the threshold was PDC of at least 0.70 (instead of

at least 0.80), and fewer patients were adherent if the cut-off was PDC of at least 0.90 (Figure 1).

DISCONTINUATION

Rates of discontinuation of the index oral anticancer agent are displayed in Table 4. Patients with CML had the lowest rates of discontinuation (32%), followed by patients with mPC (38%) and mRCC (42%). Discontinuation rates were higher for patients with MM (48%) and mBC (58%). Median time to discontinuation of index oral anticancer agent among patients who discontinued was between 84 days for patients with CML, 98 days for patients with MM, 120 days for patients with mPC, 84 days for patients with mRCC, and 103 days for patients with mBC. There was substantial variation in these outcomes across the individual index oral anticancer agents for some of the cancers (Table 4).

Discussion

To our knowledge, this is the first study that offers a wide-ranging assessment of treatment utilization patterns with newly initiated oral anticancer agents across multiple cancers and therapies in a national sample of US Medicare beneficiaries. As such, it offers several insights that add to our understanding of utilization patterns in this population and provides a valuable benchmark for stakeholders seeking to measure and improve adherence to oral anticancer agents.

Our study is among the first to report on the nontrivial proportion of cancer patients who filled only a single prescription for their index oral anticancer agent. More than 1 in 5 patients with mRCC, 1 in 6 patients with MM, and 1 in 10 patients with mPC and CML had only a single fill of their index agent. Our findings on the number of 30-day supply prescriptions suggested that even among those who

TABLE 3 Adherence to Index Oral Anticancer Agents in the Post-Index Period

Type of cancer and oral anticancer agent	All patients n	PDC measured over 365 days post-index or until death/hospice for index oral anticancer agent		Patients with >1 fill of index oral anticancer agent n	PDC measured between first fill to last fill among those with >1 fill for index oral anticancer agent	
		PDC mean (SD)	PDC ≥ 0.80 %		PDC mean (SD)	PDC ≥ 0.80 %
CML	1,650	0.69 (0.32)	884 (54)	1,459	0.85 (0.19)	1,074 (74)
Bosutinib	a	0.41 (0.41)	a	a	0.90 (0.14)	a
Dasatinib	429	0.66 (0.34)	216 (50)	363	0.86 (0.20)	274 (75)
Imatinib	846	0.73 (0.30)	493 (58)	764	0.86 (0.18)	577 (76)
Nilotinib	344	0.67 (0.32)	172 (50)	306	0.82 (0.21)	208 (68)
Ponatinib	a	0.49 (0.24)	a	a	0.80 (0.17)	a
MM	7,461	0.58 (0.31)	2,585 (35)	6,182	0.79 (0.20)	3,600 (58)
Lenalidomide	6,518	0.59 (0.31)	2312 (35)	5,453	0.79 (0.20)	3,154 (58)
Pomalidomide	368	0.62 (0.29)	126 (34)	298	0.79 (0.19)	159 (53)
Thalidomide	575	0.50 (0.32)	147 (26)	431	0.82 (0.22)	287 (67)
mPC	6,998	0.69 (0.29)	3,347 (48)	6,127	0.92 (0.15)	5,302 (87)
Abiraterone	5,585	0.69 (0.30)	2631 (47)	4,877	0.92 (0.15)	4,232 (87)
Enzalutamide	1,413	0.71 (0.28)	716 (51)	1,250	0.91 (0.15)	1,070 (86)
mRCC	2,553	0.61 (0.33)	981 (38)	1,835	0.87 (0.18)	1,365 (74)
Axitinib	313	0.65 (0.30)	130 (42)	242	0.86 (0.18)	174 (72)
Pazopanib	851	0.54 (0.34)	262 (31)	608	0.85 (0.20)	431 (71)
Sorafenib	175	0.57 (0.33)	56 (32)	118	0.82 (0.19)	75 (64)
Sunitinib	1,214	0.65 (0.32)	484 (40)	867	0.86 (0.19)	685 (79)
mBC	79	0.52 (0.29)	17 (22)	46	0.86 (0.16)	46 (70)
Lapatinib	a	0.43 (0.28)	a	a	0.85 (0.17)	12 (75)
Everolimus	a	0.56 (0.28)	a	a	0.86 (0.16)	34 (68)

*Cell sizes with $n < 11$ omitted to comply with the Centers for Medicare and Medicaid Services' cell size suppression policy.

CML = chronic myeloid leukemia; mBC = metastatic breast cancer; MM = multiple myeloma; mPC = metastatic prostate cancer; mRCC = metastatic renal cell carcinoma; PDC = proportion of days covered.

were alive during the entire 12 months of follow-up, the average number of 30-day prescriptions ranged from as low as 6 (mRCC and mBC) to almost 9 (CML and mPC).

In some cases, the high rates of single fills and low number of prescription fills could be due to toxicities of certain oral agents, such as those for mBC and mRCC, wherein the latter have been shown to lead to discontinuation or therapy switching in the first month of treatment.^{22,23} Other factors such as social determinants of health may also be at play. As toxicities and disease progression will always necessitate that some patients stop medications after 1 fill, the optimal number of patients with only 1 fill will vary by disease and therapy type and will never be zero. However, payers and pharmacies may find these data to be useful

benchmarks in determining whether quality issues like toxicity management may be suboptimal in their patient populations.

Clinicians may also find these data useful as they initiate patients on new oral anticancer treatments, directing clinical attention to adherence and toxicity management. Refill behavior for oral anticancer agents in clinical practice is significantly more difficult to track relative to traditional intravenous cancer treatments, in which missed clinic or office visits can immediately signal an issue to providers. Our findings also inform and have implications for budget impact modeling and economic analyses wherein clinical trial-based assumptions on the number of prescriptions to be filled (and hence total treatment costs) for a new

FIGURE 1 Sensitivity Analysis Using Alternative Cut-Offs to Define Adherence to Index Oral Anticancer Agents in the Post-Index Period**A. PDC measured over 365 days post-index or until death/hospice for index oral anticancer agent** **B. PDC measured between first fill to last fill among those with >1 fill for index oral anticancer agent**

CML=chronic myeloid leukemia; mBC=metastatic breast cancer; MM=multiple myeloma; mPC=metastatic prostate cancer; mRCC=metastatic renal cell carcinoma; PDC=proportion of days covered.

oral anticancer agent over a 12-month period may grossly overestimate treatment utilization patterns in real-world practice.

Our evaluation of adherence using the PDC measure revealed several important findings. From a methodological perspective, calculating adherence using a modified PDC measured between first and last fill of the oral anticancer agent yielded higher adherence rates than a traditional PDC calculated based on a fixed period. As the median progression-free survival for many of the drugs in our study is less than a year (ie, most patients will need to change treatment within 12 months), our modified PDC measure based on first and last fills is likely a better representation of patient adherence. The first and last fill date may also better capture provider intention to change treatment than a fixed time interval: a physician may have tried a therapy for several months before deciding a patient was a better candidate for another therapy, perhaps due to toxicities or disease progression. This finding has

obvious methodological implications for future studies or interventions using claims data to track adherence to oral anticancer medications.

From a clinical perspective, it was concerning to find that even with this modified PDC measure, adherence to the oral anticancer agent was still suboptimal. Even for a cancer like CML, wherein daily oral TKI use has been shown to permit near-normal life expectancy, between 25% (or 1 in 4) and 32% (or 1 in 3) of patients were not adherent.²⁴ Adherence rates based on the modified PDC were the highest for oral anticancer agents for mPC, likely reflecting the relatively benign side effect profile of these agents compared to the other medications in this study, but even then, 1 in 7 patients were not adherent. On the other hand, adherence was poorest for MM, with almost half to one third of patients not being adherent between their first and last fill. However, dose reductions and treatment breaks are common with these myeloma therapies but not readily perceptible in claims data. Thus, the

TABLE 4 Discontinuation of Index Oral Anticancer Agents in the Post-Index Period

Type of cancer and oral anticancer agent	All patients n	Discontinuation of index oral anticancer agent n (%)	Time to discontinuation (days) among those who discontinued, median
CML	1,650	525 (32)	84
Bosutinib	^a	^a	60
Dasatinib	429	156 (36)	64
Imatinib	846	238 (28)	90
Nilotinib	344	110 (32)	79
Ponatinib	^a	14 (67)	154
MM	7,461	3,544 (48)	98
Lenalidomide	6,518	3,093 (47)	102
Pomalidomide	368	140 (38)	105
Thalidomide	575	311 (54)	84
mPC	6,998	2,638 (38)	120
Abiraterone	5,585	2,169 (39)	120
Enzalutamide	1,413	469 (33)	120
mRCC	2,553	1,080 (42)	84
Axitinib	313	110 (35)	96
Pazopanib	851	401 (47)	61
Sorafenib	175	71 (41)	90
Sunitinib	1,214	498 (41)	88
mBC	79	46 (58)	103
Lapatinib	^a	16 (73)	112
Everolimus	^a	30 (53)	101

^aCell sizes with n < 11 were omitted to comply with the Centers for Medicare & Medicaid Services' cell size suppression policy.

CML = chronic myeloid leukemia; mBC = metastatic breast cancer; MM = multiple myeloma; mPC = metastatic prostate cancer; mRCC = metastatic renal cell carcinoma.

apparently lower adherence may partially reflect patients taking fewer pills or longer breaks at the direction of their oncologist. Nevertheless, these findings provide a helpful benchmark for comparison in other studies that use a similar methodology. While a PDC threshold of 0.80 for deeming patients as being adherent may make sense for many chronic diseases and certain cancers like CML, the variable dosing regimens, toxicities, and methodologic challenges of measuring adherence to anticancer therapies

may warrant using different thresholds for other cancers such as MM and mRCC. Future studies should identify disease-specific adherence thresholds that reflect these realities and use those thresholds as targets for quality improvement.

Finally, we also found high discontinuation rates of the index oral anticancer agent across most cancers. Anticancer drugs may be discontinued for a number of reasons. A longer length of treatment-free interval may be a sign of cancer remission due to

a good response to the index agent. However, patients may also discontinue the index agent and switch to another cancer treatment due to toxicity or disease progression. While examination of switching to another treatment among those who discontinued their index oral anticancer agent was beyond the scope of this study, especially given the prevalence of off-label use in this setting, we conducted post hoc exploratory analyses using a simplistic approach to identify discontinuers who received any subsequent anticancer drug (oral, injectable, or infusible), regardless of the approved indication of the agent or when it was initiated.

Our additional exploratory analyses found many of the patients who discontinued their index oral anticancer agent also had evidence of use of a different anticancer agent during the post-index period (79% CML, 71% MM, 95% mPC, 65% mRCC, 98% mBC; data not shown). In the case of the treatments for MM, mBC, and mPC, the use of other agents is typically concomitant with the index agent; in the other cancers that we studied, it is likely that some of the patients who discontinued the oral anticancer agent may have switched to another treatment due to progression and/or toxicity with the index agent. For instance, we found that all patients with CML who started and subsequently discontinued imatinib took a different oral cancer agent during the post-index period (100%), which likely represents switching to a newer generation of oral CML therapies.

Among patients with mRCC who discontinued their medication, 53% received another oral cancer agent, while 18% received an IV agent during the post-index period, likely representing therapy change, as combination therapy was not used widely during the study period. Nevertheless, the findings raise concerns that

suboptimal adherence to the initial (index) oral anticancer agent as measured by the modified PDC between the first and last fill may have contributed to disease progression and the resultant discontinuation of the initial oral agent and switch to a different treatment, as some studies have demonstrated.²⁴

Although there is no consensus on what constitutes ideal adherence to these oral oncology therapies, our study may provide useful real-world adherence benchmarks for interventions being pursued to improve treatment adherence given the association of lower adherence with poor cancer outcomes. Clinicians, pharmacists, and payers may use our study findings to further direct efforts to identify and target low adherence in their patient populations and tailor strategic interventions given limited resources. For instance, oncology practices should ask their patients about adherence to oral anticancer therapies and do so in a nonjudgmental fashion, with particular emphasis on barriers to adherence, such as cost and side effects. Early and aggressive toxicity management (eg, hand foot syndrome with sorafenib) may also help improve adherence and persistence to effective medications.^{25,26}

Physician practices could also take a more proactive role in helping patients navigate the costs of cancer care through the use of an office financial counselor to assist in obtaining financial assistance.²⁷ Similarly, pharmacist-led interventions may include follow-up evaluations with patients shortly after starting therapy and reminders to refill medication after their first cycle—a particularly important consideration given that many patients in our study only filled a single prescription.²⁸ In fact, the recently published best practices for the management of oral anticancer therapies from the Hematology/Oncology Pharmacist Association (HOPA) could lead to an expanded role for the pharmacist at several points along the care continuum.²⁹

Payers may also consider the possibility of more comprehensive solutions such as a cycle management program, which focuses on “providing specialized counseling and monitoring for patients to improve their therapy experience.”³⁰ Such programs are increasingly being pursued by payers through their specialty pharmacies, and these programs offer services such as prescription refill reminders, advice on potential side effects, and alerts for physicians when a patient is not picking up their medication.³¹⁻³⁴

Specialty pharmacies can inquire about barriers to adherence when coordinating a refill with the patient, particularly if the refill has been delayed. They may also offer synchronization services, where patients taking multiple oral medications have all of their medications filled at the same time each month, which have also demonstrated some promise at improving adherence.³⁵ Specialty pharmacies

can also play a role in alleviating the financial burden placed on patients by high drug costs through programs to help patients identify and apply for financial assistance.³⁶

Finally, there are also potential policy solutions to improve adherence by limiting the out-of-pocket costs of oral anticancer therapies under Medicare Part D. Several stakeholders have called for the institution of an annual out-of-pocket maximum and “smoothing out” of the cost sharing under Part D³⁷; however, these proposals have only recently been introduced in Congress, and their future remains uncertain.

LIMITATIONS

Our study had several limitations that deserve mention. First, as a retrospective study using insurance claims data, reasons for nonadherence and discontinuation were unavailable (eg, disease progression, treatment response, side effects). Thus, we are unable to comment on the appropriateness of nonadherence and discontinuation. Relatedly, our descriptive analysis results should not be taken as a guide to what optimal adherence should be. There likely isn't a “one-size-fits-all” adherence target (eg, PDC ≥ 0.80), and a more comprehensive view would determine the role of “thoughtful nonadherence,” which might also include a range of alternative treatment options, including palliative care.

Second, although our adherence and discontinuation outcomes were based on widely accepted measurement methods with administrative claims, they are unable to capture whether a medication was actually taken as prescribed or not.

Third, we adjusted the days supply for some drugs for mRCC and MM given the dosing schedules of these drugs. While this was done to avoid misestimation of our outcome measures, we acknowledge that we had to make assumptions in the absence of how the drugs had been actually prescribed and cannot account for further dosing adjustments made by providers that are not captured in claims data.

Fourth, as with all claims analyses, data may be subject to coding errors. Fifth, claims data are only available for the Medicare FFS patients and hence our findings may not be generalizable to the Medicare Advantage population. Sixth, the scope of this study did not include assessing the factors associated with oral anticancer treatment utilization patterns and their impact on clinical outcomes, health resource use, and costs.

Finally, the national Medicare claims data available to the team at the time of the analysis was only until 2014. Several new oral anticancer agents have entered the market since then for some of the cancers (eg, breast cancer)

examined in our study and should be evaluated in future studies using more recent data.

Conclusions

Our study provides a comprehensive assessment of treatment utilization patterns in US Medicare patients initiating oral anticancer treatments with direct implications for clinical practice and policy. As the proliferation of innovative oral anticancer therapies is likely to continue unabated, further research is urgently needed to examine factors associated with non-adherence to oral anticancer agents in Medicare patients and develop and test interventions to address these barriers.

DISCLOSURES

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Brown is employed by Humana, Inc., and Ward was employed by Humana, Inc., from research inception through initial drafts. Doshi has served as an advisory board member or consultant for Allergan, Ironwood Pharmaceuticals, Janssen, Kite Pharma, Merck, Otsuka, Regeneron, Sarepta, Sage Therapeutics, Sanofi, and Vertex and has received research funding from AbbVie, Biogen, Humana, Janssen, Novartis, PhRMA, Regeneron, Sanofi, and Valeant. Her spouse holds stock in Merck and Pfizer. All other authors have no financial conflicts of interest to report.

REFERENCES

- Sasaki K, Strom SS, O'Brien S, et al. Relative survival in patients with chronic-phase chronic myeloid leukaemia in the tyrosine-kinase inhibitor era: analysis of patient data from six prospective clinical trials. *Lancet Haematol*. 2015;2(5):186.
- Mandal R, Bolt DM, Shah BK. Disparities in chronic myeloid leukemia survival by age, gender, and ethnicity in pre- and post-imatinib eras in the US. *Acta Oncol*. 2013;52(4):837-41.
- May P, LaPlant K, McGee A. Practice model: establishing and running an oral chemotherapy management clinic. *Asia Pac J Oncol Nurs*. 2017;4(4):299-303.
- Greer JA, Amoyal N, Nisotel L, et al. A systematic review of adherence to oral antineoplastic therapies. *Oncologist*. 2016;21(3):354-76.
- Puts MT, Tu HA, Tourangeau A, et al. Factors influencing adherence to cancer treatment in older adults with cancer: a systematic review. *Ann Oncol*. 2014;25(3):564-77.
- Mathes T, Pieper D, Antoine SL, Eikermann M. Adherence influencing factors in patients taking oral anticancer agents: a systematic review. *Cancer Epidemiol*. 2014;38(3):214-26.
- Mislang AR, Wildes TM, Kanesvaran R, et al. Adherence to oral cancer therapy in older adults: The International Society of Geriatric Oncology (SIOG) taskforce recommendations. *Cancer Treat Rev*. 2017;57:58-66.
- Mato A, Jahnke J, Li P, et al. Real-world treatment and outcomes among older adults with chronic lymphocytic leukemia before the novel agents era. *Haematologica*. 2018;103(10):e465.
- American Cancer Society. Key statistics about kidney cancer. January 4, 2018. Accessed August 16, 2021. <https://www.cancer.org/cancer/kidney-cancer/about/key-statistics.html>
- American Cancer Society. Key statistics for chronic lymphocytic leukemia. January 8, 2019. Accessed August 16, 2021. <https://www.cancer.org/cancer/chronic-lymphocytic-leukemia/about/key-statistics.html>
- American Cancer Society. Key statistics for chronic myeloid leukemia. January 8, 2019. Accessed August 16, 2021. <https://www.cancer.org/cancer/chronic-myeloid-leukemia/about/statistics.html>
- American Cancer Society. Key statistics for prostate cancer. January 8, 2019. Accessed August 16, 2021. <https://www.cancer.org/cancer/prostate-cancer/about/key-statistics.html>
- American Cancer Society. Key statistics for prostate cancer. February 28, 2018. Accessed August 16, 2021. <https://www.cancer.org/cancer/multiple-myeloma/about/key-statistics.html>
- Murthy VH, Krumholz HM, Gross CP. Participation in cancer clinical trials: race-, sex-, and age-based disparities. *JAMA*. 2004;291(22):2720-26.
- Mallick R, Cai J, Wogen J. Predictors of non-adherence to systemic oral therapy for advanced hepatocellular carcinoma. *Curr Med Res Opin*. 2013;29(12):1701-08.
- Dusetzina SB, Winn AN, Abel GA, Huskamp HA, Keating NL. Cost sharing and adherence to tyrosine kinase inhibitors for patients with chronic myeloid leukemia. *J Clin Oncol*. 2014;32(4):306-11.
- Seal BS, Anderson S, Shermock KM. Factors associated with adherence rates for oral and intravenous anticancer therapy in commercially insured patients with metastatic colon cancer. *J Manag Care Spec Pharm*. 2016;22(3):227-35. doi:10.18553/jmcp.2016.22.3.227
- Winn AN, Dusetzina SB, Keating NL. Factors associated with tyrosine kinase inhibitor initiation and adherence among Medicare beneficiaries with chronic myeloid leukemia. *J Clin Oncol*. 2016;34(36):4323-28.
- Shen C, Zhao B, Liu L, Shih YT. Adherence to tyrosine kinase inhibitors among Medicare Part D beneficiaries with chronic myeloid leukemia. *Cancer*. 2018;124(2):364-73.
- MacLean E, Mardekian J, Cisar LA, et al. Real-world treatment patterns and costs for patients with renal cell carcinoma initiating treatment with sunitinib and pazopanib. *J Manag Care Spec Pharm*. 2016;22(8):979-90. doi:10.18553/jmcp.2016.22.8.979

21. Vogelzang NJ, Pal SK, Ghate SR, et al. Real-world economic outcomes during time on treatment among patients who initiated sunitinib or pazopanib as first targeted therapy for advanced renal cell carcinoma: a retrospective analysis of Medicare claims data. *J Manag Care Spec Pharm.* 2018;24(6):525-33. doi:10.18553/jmcp.2018.24.6.525
22. Di Lorenzo G, Porta C, Bellmunt J, et al. Toxicities of targeted therapy and their management in kidney cancer. *Eur Urol.* 2011;59(4):526-40.
23. Bekker CL, Melis EJ, Egberts ACG, et al. Quantity and economic value of unused oral anti-cancer and biological disease-modifying anti-rheumatic drugs among outpatient pharmacy patients who discontinue therapy. *Res Social Adm Pharm.* 2019;15(1):100-05.
24. Ganesan P, Sagar TG, Dubashi B, et al. Nonadherence to imatinib adversely affects event free survival in chronic phase chronic myeloid leukemia. *Am J Hematol.* 2011;86(6):471-74.
25. Scandurra G, Aiello RA, Ali M, et al. Appropriate management of cutaneous adverse events maximizes compliance with sorafenib treatment: a single-center experience. *Future Oncol.* 2012;8(5):609-15.
26. Jasim S, Iniguez-Ariza NM, Hilger CR, et al. Optimizing lenvatinib therapy in patients with metastatic radioactive iodine-resistant differentiated thyroid cancers. *Endocr Pract.* 2017;23(10):1254-61.
27. McNamara E, Redoutey L, Mackler E, et al. Improving oral oncolytic patient self-management. *J Oncol Practice.* 2016;12(9):e864-69.
28. Felton MA, van Londen GJ, Marcum ZA. Medication adherence to oral cancer therapy: the promising role of the pharmacist. *J Oncol Pharm Pract.* 2016;22(2):378-81.
29. Mackler E, Segal EM, Muluneh B, et al. 2018 Hematology/Oncology Pharmacist Association best practices for the management of oral oncolytic therapy: pharmacy practice standard. *J Oncol Pract.* 2019;15(4):e346-e55.
30. Deutsch S, Koerner P, Miller RT, et al. Utilization patterns for oral oncology medications in a specialty pharmacy cycle management program. *J Oncol Pharm Pract.* 2016;22(1):68-75.
31. Suchanek, D. The rise and role of specialty pharmacy. *Biotechnol Healthc.* 2005;2(5):31-35.
32. Dong X, Fetterolf D. Specialty pharmacy: an emerging area of interest for medical management. *Dis Manag.* 2005;8(2):3-85.
33. Calla, N. What is a specialty pharmacy? Specialty Pharmacy Times. December 18, 2013. Accessed August 16, 2021. https://www.pharmacytimes.com/publications/specialty-pharmacy-times/2013/nov_dec-2013/what-is-a-specialty-pharmacy
34. Advisory Board. Specialty pharmacy, explained. 2018. Accessed August 16, 2021. <https://www.advisory.com/research/care-transformation-center/care-transformation-centerblog/2018/03/specialty-pharmacy>
35. Girdish C, Shrank W, Freytag S, et al. The impact of a retail prescription synchronization program on medication adherence. *J Am Pharm Assoc.* 2017;57(5):579-84.
36. James D. The importance of financial counseling services for patients with cancer. 2019. Accessed August 16, 2021. <https://www.pharmacytimes.com/publications/directions-in-pharmacy/2019/september2019/the-importance-of-financial-counseling-services-for-patients-with-cancer>
37. Doshi JA, Pettit AR, Li P. Addressing out-of-pocket specialty drug costs in Medicare Part D: the good, the bad, the ugly, and the ignored. *Health Affairs Blog.* July 25, 2018. Accessed August 16, 2021. <https://www.healthaffairs.org/doi/10.1377/hblog20180724.734269/full/>