Tyrosine Kinase Inhibitors Initiation, Cost Sharing, and Health Care Utilization in Patients with Newly Diagnosed Chronic Myeloid Leukemia: A Retrospective Claims-Based Study

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ABSTRACT

BACKGROUND: For newly diagnosed chronic myeloid leukemia (CML) patients, early access to tyrosine kinase inhibitors (TKIs) is a consistent predictor of adherence and optimal response. The expense of targeted therapies, however, may result in high out-of-pocket costs for initiating therapy that could be a barrier to starting treatment.

OBJECTIVE: To examine the association between TKI out-of-pocket costs, initiation, and health care utilization and costs among patients who initiated TKI within 12 months after initial CML diagnosis.

METHODS: Individuals aged 18-64 years with an initial diagnosis of CML were identified in the IBM MarketScan Commercial Database between April 11, 2011, and December 31, 2014. The association between cost sharing and TKI initiation was evaluated using a multivariable logistic regression model applied to patients receiving therapy within a month of diagnosis and within 1-12 months after diagnosis. Health care utilization was compared using negative binomial regression models. Health care cost differences between the 2 patient groups were estimated using generalized linear models. All models were controlled for potential confounding factors.

RESULTS: The study sample consisted of 477 patients, with 397 (83.2%) patients initiating TKI within the first month of CML diagnosis and 80 (16.8%) after the first month. Out-of-pocket costs for the initial 30-day supply of TKI medications were not found to be a significant predictor of TKI initiation time. Patients initiating therapy within a month were less likely to have all-cause hospitalizations (IRR = 0.35; $P = 0.02$) or CML-specific hospitalizations (IRR = 0.27; $P < 0.01$). Over the 12-month follow-up period, they incurred \$9,923 more in TKI pharmacy costs ($P < 0.05$), but patients initiating therapy after the first month of diagnosis incurred \$7,582 more in medical costs, \$218 more in non-TKI pharmacy costs, and \$2,680 more in total health care costs ($P > 0.05$).

CONCLUSIONS: Patients with TKI initiation within the first month of diagnosis had higher TKI pharmacy costs that were partially offset by lower medical and non-TKI pharmacy costs, resulting in lower overall total health care costs. Findings suggest that earlier TKI initiation may reduce the risks of hospitalizations, which could result in potential medical cost savings in the first 12 months of treatment.

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What is already known about this subject

- Chronic myeloid leukemia (CML) patients are required to take their daily dose of oral tyrosine kinase inhibitors (TKIs) indefinitely for long-term survival.
- Patients initiating anticancer drugs face high out-of-pocket costs because prescription drug plans in the United States tend to have cost-sharing mechanisms in order to control the high costs of these medications.
- Despite the high costs of TKIs, CML patients gain significant health improvements from their optimal use.

What this study adds

- Commercial insurance claims data were used to show the association between the timing of TKI initiation and health care utilization and costs in patients newly diagnosed with CML.
- Patients with earlier TKI initiation had lower risk of hospitalizations.
- Patients with earlier TKI initiation had higher TKI pharmacy costs that were partially offset by lower medical and non-TKI pharmacy costs, resulting in lower overall total health care costs.

Chronic myeloid leukemia (CML) accounts for 15% of all leukemias in adults.¹ In 2019, an estimated 8,990 people are expected to be diagnosed with CML in the United States, and 1,140 people are expected to die from the disease.² CML is usually diagnosed in the chronic phase, but if left untreated, the disease will eventually progress to the advanced phase (accelerated or blast) in less than 5 years.^{1,3} The National Comprehensive Cancer Network recommends imatinib, dasatinib, and nilotinib as first-line tyrosine kinase inhibitor (TKI) therapy for newly diagnosed patients with chronic phase CML.¹ Imatinib was the first TKI approved and has been considered the standard of care for more than a decade, whereas second-generation TKIs, namely dasatinib and nilotinib, are highly effective with observed improvements in progression-free survival and overall survival in newly diagnosed patients and those who fail imatinib.^{4,5} Alternative second- and third-generation TKIs, bosutinib and ponatinib, have also become available as second-line options.^{1,4,5}

Imatinib and other TKIs have revolutionized the management of CML, making it possible for most CML patients treated with TKIs to experience near normal life expectancy, especially if they were diagnosed before age 65.^{6,7} Patients are required to be adherent to their TKI therapy to achieve optimal response and prevent disease progression.⁸⁻¹⁰ In addition to adherence, newly diagnosed CML patients who started imatinib within 6 months of diagnosis while in the first chronic phase show sustained responses and higher overall survival at a 5-year follow-up.¹¹ Other studies have shown that cytogenetic and molecular responses, progression-free survival, and event-free survival may be inferior in patients who start imatinib more than 6 months after diagnosis.¹²⁻¹⁵ Early prescribing has also been a consistent predictor of adherence.¹⁶ Hence, when indicated, a prescription for TKI therapy should be provided promptly after CML diagnosis because studies have found that time since diagnosis for initiation of TKI therapy was associated with the CML patient's level of medication adherence.¹⁶⁻¹⁸ A longer time lag between CML diagnosis and the fill of the first TKI prescription was associated with higher rates of nonadherence.^{8,19} In addition, studies show that nonadherence to treatment may be associated with high annual health care costs, since it decreases treatment effectiveness.²⁰⁻²²

All of these studies underscore the importance of initial access to TKI for patients newly diagnosed with CML who require prompt treatment.²³ Given the expense of these targeted therapies, out-of-pocket costs for initiating therapy may be high and could act as a barrier to starting treatment. In the United States, patients may be subject to out-of-pocket payments of 20% of drug prices, which could amount to \$20,000-\$30,000 annually.²⁴ Hence, prescription coverage can become quite costly for cancer patients and having a prescription drug plan does not necessarily mean that it covers all costs for the drugs needed.²⁵

In this study, we examined the association between timing of TKI initiation and cost sharing, health care utilization, and costs in commercially insured patients with newly diagnosed CML.

Methods

Data Source

This retrospective claims-based study was conducted using longitudinal medical and pharmacy claims data from employer-based, commercially insured group health plans in the United States, covering subscribers and dependents up to age 65. We used the IBM MarketScan Commercial Database from January 1, 2011, to December 31, 2015. The MarketScan database captured person-specific clinical utilization, expenditures, and enrollment across inpatient, outpatient, and prescription drug services. All data were deidentified in accordance with the Health Insurance Portability and Accountability Act (HIPAA) requirements.

Sample Selection

Patients were included if they had at least 1 inpatient or 2 outpatient claims (at least 30 days apart) with a diagnosis of CML between April 1, 2011, and December 31, 2014 (the first of which represented the index claim). CML diagnosis was defined using the *International Classification of Diseases, Ninth Revision, Clinical Modification* [ICD-9-CM] code for chronic myeloid leukemia (205.1X) or *International Classification of Diseases, Tenth Revision, Clinical Modification* [ICD-10-CM] code for chronic myeloid leukemia (C92.1X).

Patients were excluded if they (a) were aged younger than 18 years at the index claim date or turned age 65 during the study period; (b) had no continuous enrollment in the health plan in the 3 months before and 12 months after the index claim; (c) had no drug benefit; (d) had any claim for a TKI preceding CML diagnosis; (e) had no claim for a molecular oncogene diagnostic test (during the 30 days before or after the index claim); (f) had not initiated a TKI within 12 months of CML diagnosis; and (g) had no continuous enrollment in the health plan and drug benefit during the 12 months after TKI initiation (Figure 1).

Study Variables

Measure for TKI Out-of-Pocket Costs. The mean out-of-pocket costs were calculated for the first 30-day supply of TKI medication. Out-of-pocket costs were defined as the sum of the copayments, coinsurance, and deductibles paid by the patient at the time that the first TKI prescription was filled. The mean out-of-pocket costs per patient were used, along with other patient characteristics, to predict timing of TKI initiation.

Measure for TKI Initiation. The variable measured the time to TKI initiation, defined as the number of months elapsed between the index claim date (first CML diagnosis claim during the study period) and the date that the first TKI prescription was filled during the 12-month post-index period. All TKIs approved for CML and available during the 2011-2015 study period (imatinib [Gleevec], dasatinib [Sprycel], nilotinib [Tasigna], bosutinib [Bosulif], and ponatinib [Iclusig]) were included in the measure definition.

Clinical benefits are most likely to occur when CML patients initiate TKI within 6 months after diagnosis, but patients are expected to begin treatment as soon as they have been diagnosed for optimal response.^{1,11-15} For the purpose of our study, patients were classified as early initiators of TKI if they had a first claim for a TKI prescription within the first month of CML diagnosis. They were considered to have delayed TKI initiation if their first claim for a TKI prescription occurred after a month of diagnosis and before the end of the 12-month post-index period.

FIGURE 1 Study Cohort Selection and Subject Exclusion

CML=chronic myeloid leukemia; ICD-9/10 CM=International Classification Diseases, Ninth/Tenth Revision, Clinical Modification; TKI=tyrosine kinase inhibitor.

Outcomes

Annual Health Care Utilization. Five distinct utilization measures were assessed during the 12-month follow-up period from TKI initiation: (1) number of outpatient physician visits; (2) number of emergency room [ER] visits; (3) number of all-cause hospitalizations; (4) number of CML-specific hospitalizations (identified as any inpatient admission with an ICD-9-CM

or ICD-10-CM code for CML as the primary or secondary diagnosis); and (5) number of prescriptions.

Annual Health Care Costs. Health care costs during the 12-month follow-up period from TKI initiation are reflected in the allowed amount, which is equal to the sum of plan paid, coordination of benefits, and patient out-of-pocket costs, including copayments, coinsurance, and deductibles. Four distinct cost variables were reported:

(1) medical costs, (2) TKI pharmacy costs, (3) non-TKI pharmacy costs, and (4) total all-cause health care costs, representing aggregated medical and pharmacy costs.

Costs (in U.S. dollars) were converted to 2015 values using the medical component of the Consumer Price Index.

Covariates

We reported demographic characteristics as of the index claim date, such as patient age; sex; year of the index claim; health plan type (comprehensive, preferred provider organization, point of service, consumer-driven health plan/high deductible health plan, exclusive provider organization, and health maintenance organization); region of residence (Northeast, North Central, South, and West); and the patient's relationship to subscriber (subscriber vs. spouse or dependent).

We identified clinical characteristics using all available medical and pharmacy claims for study patients in the 3-month pre-index period. These included a Deyo-Charlson Comorbidity Index score as a measure of comorbidity burden,²⁶ the number of unique drug classes filled as a measure of pill burden, and Darkow CML Complexity Index score (categorized as usual, moderate, or high, using reported diagnoses of associated complications, comorbidities, or adverse events) as a measure of the difficulty of managing the patient's disease.²²

The starting dose of the index TKI medication was used as a proxy for the phase of CML disease.^{22,27} This dose was calculated as the strength of TKI dispensed multiplied by the quantity filled, divided by the days supply on the pharmacy claim. For imatinib, the starting dose was categorized as ≤ 400 mg (i.e., the typical starting dose for chronic phase CML) or ≥ 600 mg (i.e., the typical starting dose for accelerated phase or blast crisis).²⁸ For dasatinib, the starting dose was categorized as ≤ 100 mg (i.e., the typical starting dose for chronic phase CML) or ≥ 140 mg (i.e., the typical starting dose for advanced phase).²⁹ For nilotinib, the starting dose was categorized as ≤ 600 mg (i.e., the typical starting dose for chronic phase CML) or ≥ 800 mg (i.e., the typical starting dose for accelerated phase).³⁰ For bosutinib, the starting dose was categorized as ≤ 500 mg (i.e., the typical starting dose for chronic, accelerated, or blast phase CML in patients resistant to or intolerant to other therapies, including imatinib).³¹ For ponatinib, the starting dose was categorized as ≤ 45 mg (i.e., the typical starting dose for chronic, accelerated, or blast phase CML in patients for whom no other TKI therapy is indicated).³²

An indicator variable for whether the patient was adherent to TKI during the 12-month follow-up was used. We estimated patient adherence to TKI using the proportion of days covered (PDC).³³ Patients were classified as adherent to TKIs if they had a PDC of at least 80%, when they were most likely to achieve clinical benefits from their treatment.⁸⁻¹⁰ We used an indicator variable for whether the patient had any TKI dose decrease as a proxy for TKI adverse events during the 12-month follow-up

period because TKI toxicities are managed by decreasing the initial dose prescribed.¹ The other control variable was mean out-of-pocket costs paid by the patient for inpatient and outpatient services and non-TKI pharmacy medications for the entire 12-month follow-up period.

Statistical Analyses

We conducted statistical comparisons between the characteristics of patients who initiated TKI therapy within 1 month (early initiators) and 1-12 months (late initiators) of CML diagnosis using the Wilcoxon-Mann-Whitney test for continuous variables and Pearson's chi-square test or the Fisher's exact test (for sparse data with frequency of 5 or less) for categorical variables.

TKI Initiation. We used a multivariable logistic regression model with robust standard error estimates to calculate the odds of initiating TKI early, controlling for potential confounding factors. We determined the adjusted risk ratio (ARR) and adjusted risk difference (ARD) instead of odds ratio because TKI initiation was considered to be a common event.³⁴ The ARR is the ratio of the mean predicted probabilities and represents the probability of TKI initiation for each TKI out-of-pocket cost category after controlling for potential confounding factors.³⁵ The ARD is the difference of the mean predicted probabilities and constitutes differences in the absolute risk of initiation.³⁵

Health Care Utilization and Costs. Health care utilization was compared between the early and late initiator cohorts using unadjusted and adjusted incidence rate ratios (IRRs). Adjusted IRRs controlled for potential confounding factors and were estimated using multivariable negative binomial regression models.³⁶ No offset variable was needed because all outcome variables were observed for a full year.

Unadjusted and adjusted cost differences between the early and late initiator cohorts were estimated using multivariable generalized linear models with a gamma distribution and a log link controlling for potential confounding factors.²²

All multivariable regression analyses controlled for the same set of potential confounding factors relevant for the respective study. To study the association between TKI out-of-pocket costs and TKI initiation, the covariates used included patient age, sex, patient's relationship to subscriber, health plan type, region of residence, CML year of diagnosis, CML phase, type of TKI medication, CML complexity, Deyo-Charlson Comorbidity Index score, and number of concomitant medications. In the estimation of health care utilization and costs, the covariates used included an indicator variable of whether the patient was adherent, patient age, sex, patient's relationship to subscriber, health plan type, region of residence, TKI year of initiation, CML phase, type of TKI medication, any TKI dose decrease, CML complexity, Deyo-Charlson Comorbidity Index score, number of concomitant medications, and other out-of-pocket health care costs.

All statistical analyses were performed using STATA version 15 (StataCorp, College Station, TX). Statistical significance was assumed at P values less than 0.05. The study protocol was considered exempt by The University of Texas Health Science Center at Houston Institutional Review Board.

Results

Patient Demographic and Clinical Characteristics

There were 477 unique patients newly diagnosed with CML between April 1, 2011, and December 31, 2014, who satisfied the selection criteria for inclusion into our study. Of those, 397 (83.2%) patients were classified as early initiators for initiating TKI within a month from first CML diagnosis, with 80 (16.8%) as late initiators for initiating TKI within 1-12 months from first CML diagnosis (Figure 1).

Patient characteristics were similar in the early and late TKI initiator cohorts (Table 1). The mean age was approximately 49 years in the early initiator cohort and 48 years in the late initiator cohort, although the difference was not statistically significant ($P=0.32$). Most patients were aged 50-59 years for early and late initiators. The early initiator cohort contained a significantly ($P=0.04$) higher percentage of males than the late initiator cohort (56.2% vs. 43.8%). The majority of patients in both cohorts were enrolled in the preferred provider organization health plan type and lived in the South, which is consistent with the inherent skewness of the MarketScan dataset for these groups. Most patients in the early initiator cohort used dasatinib as their index treatment (40.0%), whereas most late initiators used imatinib (43.8%; $P=0.01$).

Statistically significant differences ($P<0.05$) were not observed for CML phase, CML complexity, comorbid conditions, or concomitant medications at baseline. Most patients were in the chronic phase of CML (94.5% of early initiators and 91.3% of late initiators) and had usual CML complexity (61.7% and 67.5%, respectively). The 10 most prevalent comorbidities found among the study cohorts are reported in Table 1.

The late initiator cohort had slightly higher mean out-of-pocket costs for the first 30-day supply of TKI medication (\$231 vs. \$190; $P<0.01$). Costs varied substantially among individuals in our sample, with 8.4% of the sample paying more than \$400—double the average amount—for the first 30-day supply of TKI. On average, copayments accounted for approximately 81.4% of the initial out-of-pocket costs for the first 30-day supply of TKI medication, while coinsurance and deductibles accounted for 13.6% and 5.0%, respectively. Without taking into account patients who had no TKI out-of-pocket costs, most of the early initiators paid \$50 or less (43.3%), whereas a majority of the late initiators incurred more than \$100 (33.8%) for their first-month supply of TKI medication.

TKI Initiation

As shown in Table 2, the only factor significantly associated with later treatment initiation was being male (ARR=0.62; 95% confidence interval [CI]=0.41-0.95).

Health Care Utilization and Costs

Late initiator patients were observed to have greater health care utilization compared with early initiator patients, particularly utilization related to outpatient physician visits, ER visits, and hospitalizations (Table 3). On an unadjusted basis, early initiator patients were less likely to have all-cause hospitalizations (IRR=0.29; $P<0.01$) and CML-specific hospitalizations (IRR=0.19, $P<0.01$). After adjusting for potential confounding factors, early initiators were much less likely to have all-cause hospitalizations (IRR=0.35; $P=0.02$) or CML-specific hospitalizations (IRR=0.27; $P<0.01$). Outpatient visits were the most frequently used health service in both study cohorts (early initiators=17.5 visits, late initiators=17.8 visits), but unadjusted and adjusted utilization did not vary between these patients ($P>0.05$).

The only significant difference found among the cost components of the total annual all-cause health care costs between the 2 study cohorts was for TKI pharmacy costs (Table 4). We found that early initiators incurred higher TKI pharmacy costs by \$9,923 ($P<0.05$).

Discussion

Most patients newly diagnosed with CML initiated TKI treatment within a month of diagnosis with no significant association with out-of-pocket costs for the first 30-day TKI supply. This finding contrasts with other retrospective cohort studies that have found the association between high cost sharing with reduced and/or delayed initiation of TKIs.^{23,37-39} These studies, however, compared the effect of cost sharing for Medicare patients between those who faced nominal cost sharing of $\leq \$5$ throughout the year if they qualified for full low-income (LIS) subsidies and fee-for-service non-LIS patients.

Our study adds to the literature by studying the relationships among out-of-pocket costs, initiation, and health care utilization and costs within a single study, which, based on a literature review, is a more comprehensive approach than those that have been used in the past. We measured actual health care utilization and costs to determine how delays in treatment affect health care utilization and overall health care costs. To the best of our knowledge, this is the first study to research the association between patient cost sharing and TKI initiation in a population of commercially insured patients newly diagnosed with CML.

In our study cohort, 14.5% had no out-of-pocket costs for their first month's supply of TKI, and the majority of patients (41.3%) incurred costs of \$50 or less. Out-of-pocket costs

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TABLE 1 Sample Characteristics by TKI Initiation Time from First CML Diagnosis

	Patients Who Initiated TKI Therapy		P Value ^a
	≤1 Month from First CML Diagnosis (n = 397)	Within >1-12 Months from First CML Diagnosis (n = 80)	
Demographic characteristics			
Age at index date, years, mean ± SD [median]	49.10 ± 10.49 [51]	47.59 ± 11.35 [49.5]	0.32
Age group, years, n (%)			0.35
18-39	71 (17.9)	21 (26.3)	
40-49	101 (25.4)	19 (23.8)	
50-59	166 (41.8)	28 (35.0)	
60-64	59 (14.9)	12 (15.0)	
Male, n (%)	223 (56.2)	35 (43.8)	0.04 ^b
Patient relationship to subscriber, n (%)			0.80
Subscriber	264 (66.5)	52 (65.0)	
Spouse or dependent	133 (33.5)	28 (35.0)	
Health plan type, n (%)			0.64
Group: comprehensive/PPO/POS/EPO	292 (73.6)	56 (70.0)	
CDHP/high deductible health plan	40 (10.1)	11 (13.8)	
HMO	37 (9.3)	9 (11.3)	
Missing/unknown	28 (7.1)	4 (5.0)	
Region of residence, n (%)			0.29
Northeast	88 (22.2)	11 (13.8)	
North Central	83 (20.9)	14 (17.5)	
South	152 (38.3)	40 (50.0)	
West	64 (16.1)	13 (16.3)	
Unknown	10 (2.5)	2 (2.5)	
Index year, n (%)			0.29
2011	101 (25.4)	26 (32.5)	
2012	111 (28.0)	26 (32.5)	
2013	95 (23.9)	14 (17.5)	
2014	90 (22.7)	14 (17.5)	
Time to drug index date from diagnosis date, days, mean ± SD [median]	12.05 ± 7.75 [11]	85.68 ± 63.08 [68.5]	<0.001 ^b
Index treatment, n (%)			0.01 ^b
Imatinib			
Started on ≤ 400 mg/day	138 (34.8)	35 (43.8)	
Started on ≥ 600 mg/day	9 (2.3)	0	
Dasatinib			
Started on ≤ 100 mg/day	157 (39.5)	21 (26.3)	
Started on ≥ 140 mg/day	2 (0.5)	0	

	Patients Who Initiated TKI Therapy		P Value ^a
	≤1 Month from First CML Diagnosis (n = 397)	Within >1-12 Months from First CML Diagnosis (n = 80)	
Index treatment, n (%)			0.01 ^b
Nilotinib			
Started on ≤ 600 mg/day	80 (20.2)	17 (21.3)	
Started on ≥ 800 mg/day	11 (2.8)	5 (6.3)	
Bosutinib			
Started on ≤ 500 mg/day	0	1 (1.2)	
Ponatinib			
Started on ≤ 45 mg/day	0	1 (1.2)	
CML chronic phase, n (%)	375 (94.5)	73 (91.3)	0.27
Darkow CML Complexity Index, n (%)			0.55
Usual	245 (61.7)	54 (67.5)	
Moderate	96 (24.2)	15 (18.8)	
High	56 (14.1)	11 (13.8)	
Deyo-Charlson Comorbidity Index, mean ± SD [median]	2.38 ± 0.96 [2]	2.59 ± 1.47 [2]	0.75
10 most prevalent comorbidities, n (%)			— ^c
Diabetes	42 (10.6)	8 (10.0)	
Chronic obstructive pulmonary disease	23 (5.8)	4 (5.0)	
Cerebrovascular	6 (1.5)	1 (1.3)	
Rheumatoid disease	6 (1.5)	1 (1.3)	
Acute myocardial	6 (1.5)	0	
Metastatic cancer	5 (1.3)	4 (5.0)	
Renal	5 (1.3)	1 (1.3)	
Congestive heart	4 (1.0)	2 (2.5)	
Peripheral vascular	4 (1.0)	1 (1.3)	
Hemiplegia/paraplegia	2 (0.5)	0	
Concomitant medications/number of unique drug classes, mean ± SD [median]	3.79 ± 3.19 [3]	3.41 ± 3.31 [3]	0.19
Out-of-pocket costs for first 30 days supply of TKI medication, \$, mean ± SD [median]	189.37 ± 683.14 [36.79]	230.24 ± 645.48 [56.06]	<0.01 ^b
Out-of-pocket costs group, n (%)			0.04 ^b
\$0	60 (15.1)	9 (11.2)	
> \$0-\$50	172 (43.3)	25 (31.2)	
> \$50-\$100	84 (21.2)	19 (23.8)	
> \$100	81 (20.4)	27 (33.8)	

^aComparing the differences between patients who initiated TKI therapy ≤ 1 month and > 1-12 months. Continuous variables were compared using the Wilcoxon-Mann-Whitney test. Categorical variables were compared using Pearson's chi-square test or the Fisher's exact test if 1 or more cells had an expected frequency of 5 or less.

^bSignificant at the 5% level.

^cP values not presented because data were too sparse.

CDHP=consumer-driven health plan; CML=chronic myeloid leukemia; EPO=exclusive provider organization; HMO=health maintenance organization; POS=point of service; PPO=preferred provider organization; SD=standard deviation; TKI=tyrosine kinase inhibitor.

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Renal	5 (1.3)	1 (1.3)	
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TABLE 2 Adjusted Risk Ratio and Adjusted Risk Difference of TKI Initiation Among Individuals with CML (n=477)

Characteristics	ARR ^a	95% CI	ARD ^a	95% CI
Mean out-of-pocket costs for first 30-day supply of TKI medication				
\$0	Reference		Reference	
> \$0-\$50	1.06	0.53 to 2.11	0.01	-0.11 to 0.13
> \$50-\$100	1.30	0.65 to 2.60	0.05	-0.09 to 0.18
> \$100	1.64	0.86 to 3.12	0.09	-0.04 to 0.22
Age at the index date, years				
18-39	Reference		Reference	
40-49	0.73	0.39 to 1.37	-0.05	-0.14 to 0.04
50-59	0.69	0.40 to 1.18	-0.06	-0.14 to 0.02
60-64	0.84	0.42 to 1.67	-0.03	-0.13 to 0.07
Male vs. female ^b	0.62	0.41 to 0.95	-0.08	-0.15 to -0.01
Subscriber (yes vs. no)	1.03	0.66 to 1.60	0.00	-0.07 to 0.08
Health plan type				
Group: comprehensive/PPO/POS/EPO	Reference		Reference	
CDHP/high deductible health plan	1.46	0.80 to 2.67	0.07	-0.06 to 0.20
HMO	1.19	0.61 to 2.33	0.03	-0.10 to 0.16
Missing/Unknown	0.98	0.39 to 2.49	-0.00	-0.15 to 0.15
Region of residence				
South	Reference		Reference	
Northeast	0.57	0.28 to 1.13	-0.08	-0.16 to 0.00
North Central	0.71	0.40 to 1.25	-0.05	-0.13 to 0.03
West	0.87	0.50 to 1.53	-0.02	-0.11 to 0.06
Unknown	0.86	0.21 to 3.46	-0.03	-0.22 to 0.18
Index year				
2011	Reference		Reference	
2012	0.88	0.53 to 1.47	-0.02	-0.10 to 0.06
2013	0.60	0.32 to 1.13	-0.07	-0.15 to 0.00
2014	0.68	0.37 to 1.24	-0.06	-0.14 to 0.02
Index treatment				
Imatinib	Reference		Reference	
Dasatinib	0.66	0.40 to 1.10	-0.06	-0.14 to 0.01
Nilotinib	1.16	0.71 to 1.90	0.03	-0.06 to 0.11
Chronic phase CML (yes vs. no)	0.82	0.36 to 1.87	-0.04	-0.20 to 0.13
Darkow CML Complexity Index				
Usual	Reference		Reference	
Moderate	0.76	0.45 to 1.26	-0.04	-0.11 to 0.03
High	1.00	0.56 to 1.78	0.00	-0.09 to 0.10
Deyo-Charlson Comorbidity Index ^c	1.24	1.00 to 1.54	0.02	0.01 to 0.04
Concomitant medications/number of unique drug classes ^c	0.98	0.91 to 1.04	-0.00	-0.02 to 0.01

^aARR and ARD were determined using a multivariable logistic regression model with robust standard error estimates.

^bSignificant at the 5% level.

^cTreated as continuous.

ARD=adjusted risk difference; ARR=adjusted risk ratio; CDHP=consumer-driven health plan; CI=confidence interval; CML=chronic myeloid leukemia; EPO=exclusive provider organization; HMO=health maintenance organization; POS=point of service; PPO=preferred provider organization; TKI=tyrosine kinase inhibitor.

for the first 30-day supply of TKI medication averaged \$198; median out-of-pocket costs were \$42 (range = \$0-\$9,443). Costs differed substantially among individuals in our sample, with 8.4% paying twice the estimated average costs for the first 30-day supply of TKI medications.

Available external funding resources for commercially insured patients may have helped in enabling them to get initiated on TKIs early after diagnosis of CML. Cancer patients can

explore resources such as the Leukemia & Lymphoma Society (LLS) Co-pay Assistance Program; patient assistance or prescription assistance programs, sponsored by major pharmaceutical manufacturers; or prescription savings programs to help finance treatment.²⁵ However, when these programs are used, the sponsored payments are not reflected in the claims data.

Future research on the effect of the use of patient assistance or prescription assistance programs on patient adherence,

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TABLE 3 Comparison of Annual Health Care Utilization Between Early and Late TKI Initiator Patients

	Average Annual Utilization (mean ± SD)		Unadjusted		Adjusted	
	Patients Who Initiated TKI Therapy		IRR ^a	P Value	IRR ^a	P Value
	≤ 1 Month from First CML Diagnosis (n = 397)	Within >1-12 Months from First CML Diagnosis (n = 80)				
Outpatient physician visits	17.49 ± 9.81	17.80 ± 14.89	0.98	0.86	1.01	0.89
Emergency room visits	0.54 ± 1.98	0.79 ± 2.11	0.69	0.29	0.73	0.27
All-cause hospitalizations	0.08 ± 0.45	0.26 ± 0.82	0.29	<0.01 ^b	0.35	0.02 ^b
CML-specific hospitalizations	0.04 ± 0.24	0.21 ± 0.77	0.19	<0.01 ^b	0.27	<0.01 ^b
Number of prescriptions (all drugs)	34.35 ± 27.22	37.60 ± 31.81	0.91	0.38	0.88	0.09
Number of TKI prescriptions	10.23 ± 3.41	9.79 ± 4.48	1.05	0.41	0.99	0.77
Number of non-TKI prescriptions	24.12 ± 26.54	27.81 ± 30.60	0.87	0.29	0.81	0.06

^aAn IRR>1 indicates that early initiators had higher incidence of incurring medical services compared with late initiators. IRRs were estimated using multivariable negative binomial regressions.

^bSignificant at the 5% level.

CML = chronic myeloid leukemia; IRR = incidence rate ratio; SD = standard deviation; TKI = tyrosine kinase inhibitor.

subsequent health care utilization, and costs will be beneficial. This is especially pertinent, since patient assistance programs are subject to availability of funds, as well as the program maximum that is imposed. For example, the LLS Co-pay Assistance Program for CML provides \$2,000.⁴⁰ The Universal Co-pay Card offered by Novartis Pharmaceuticals for Gleevec and Tasigna requires that the patient be responsible for up to the first \$25, with the remaining copay or coinsurance paid for by the program until the yearly maximum of \$15,000, after which the patient is responsible for the difference.⁴¹

Patients who initiated TKI early have correspondingly higher TKI pharmacy costs. TKIs usually account for the majority of total pharmacy costs.⁴² Our findings on total all-cause health care costs are consistent with reports using similar claims-based methodology among insured patients.²⁷ CML is a chronic disease requiring routine follow-up. As expected, outpatient visits were the most used health care, and inpatient and ER visits were low in both patient cohorts. These health care utilization patterns were consistent with other reports in the literature.^{21,22,27} The main finding is that patients who delayed initiation of TKI experienced higher levels of health care utilization. Most notably, they were much more likely to have more frequent adjusted all-cause hospitalizations and adjusted CML-specific hospitalizations (all $P < 0.05$). Future research should be done to evaluate if this finding and effect on costs is durable after the first year of TKI therapy.

Implications

Our findings have important implications. Oral anticancer medications are typically covered under a pharmacy benefit with substantial out-of-pocket costs due at the time the medication is obtained at the pharmacy.³⁸ High out-of-pocket costs for TKI medications are significantly associated with delayed

access and nonadherence.^{37,38,43} Clinical guidelines recommend initiating a TKI immediately after a diagnosis of CML, and patients using these therapies are expected to take them for a long period of time.⁴⁴ Low adherence to TKI therapy can decrease response to treatment, which can result in patients requiring stem-cell transplantation, worse clinical outcomes, and potentially shorter life expectancy.⁴⁵ In our study, we found that 51.7% of the early initiators were adherent compared with 44.4% of the late initiators. Total health care costs were higher for episodes of TKI treatment failures than those of ongoing treatment, with the costs increasing with each sequential line of TKI treatment failure.^{46,47}

This implication underscores the importance of having doctors or social workers talk with newly diagnosed CML patients about how to finance treatment and explore resources to help with their expenses. Patients should be made aware that financial support is not only available for low-income individuals. For instance, to be eligible for the LLS Co-pay Assistance Program, one has to be at or below 500% of the U.S. federal poverty guidelines as adjusted by the Cost of Living Index.⁴⁰ A single person is eligible if they have a household income at or below \$60,700, whereas a household with 4 people is eligible with an income at or below \$125,500.⁴⁰

In addition, doctors and pharmacists should focus on assessing the treatment value of different TKI therapies in relation to benefits versus cost; for instance, prescribing lower-dose dasatinib, which has at least equivalent efficacy compared with second-generation TKIs but at a significant lower cost comparable with generic imatinib.⁴⁴ Efforts to lower drug prices and, subsequently, the out-of-pocket costs for TKI medications could significantly improve adherence and overall health and economic outcomes among CML patients. Future research should focus on assessing barriers to timely access to health

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TABLE 4 Comparison of Annual Health Care Costs Between Early and Late TKI Initiator Patients

	Average Annual Costs, \$ (mean ± SD)		Unadjusted		Adjusted	
	Patients Who Initiated TKI Therapy		Cost Difference ^a [A] – [B]	P Value	Cost Difference ^a (beta coefficient)	P Value
	≤ 1 month from First CML Diagnosis (n = 397) [A]	Within > 1-12 months from First CML Diagnosis (n = 80) [B]				
Medical costs	18,022.82 ± 47,196.26	37,385.61 ± 102,911.10	-19,362.79	0.03 ^b	-7,581.78 (-.29)	0.22
TKI pharmacy costs	100,261.80 ± 32,276.67	85,516.64 ± 37,864.63	14,745.16	<0.01 ^b	9,922.02 (.11)	<0.05 ^b
Non-TKI pharmacy costs	2,580.74 ± 6,031.22	2,644.48 ± 4,655.23	-63.74	0.92	-217.17 (-.05)	0.80
Total all-cause health care costs	120,865.40 ± 57,195.23	125,546.70 ± 108,251.90	-4,681.30	0.70	-2,679.20 (-.02)	0.79

^aCost differences <0 indicate that late initiators incurred higher health care costs. Cost differences were estimated using multivariable generalized linear models with a gamma distribution and a log link.

^bSignificant at the 5% level.

CML = chronic myeloid leukemia; SD = standard deviation; TKI = tyrosine kinase inhibitor.

care for early diagnosis of CML and optimal TKI adherence to advance the understanding of and eliminate health disparities in cancer.

Limitations

We sought to minimize the limitations of administrative claims data by using multivariable regressions to control for a variety of socioeconomic and clinical characteristics that could influence treatment decisions. Other common limitations, such as missing data and errors in claims coding, may also apply in this study. Nonetheless, claims data provide a valid, big sample source of actual practice data.⁴²

The use of insurance claims data included information on filled prescriptions only, so we were unable to determine whether our large group of noninitiators did not receive a prescription, or whether they received a prescription but did not fill it. It is also possible that some patients who were classified as not initiating treatment, or as delaying initiation, may have been receiving medication via other means that would not have resulted in a prescription claim. In some cases, patients may also have supplemental cost-sharing help from patient-assistance programs, which would result in our results underestimating the true adverse affect of high cost sharing.

Much of the background outcomes information was based on the 6-month indicator. However, we classified our patients into early and late initiators using the 1-month cutoff because of the observed skewed distribution of initiators where 7 (1.47%) initiated TKI after 6 months of diagnosis. TKI initiation could have been delayed beyond 30 days by other factors such as obtaining a second medical opinion, doing additional tests, or having discussions with patients or family.

This analysis also only examined patients aged under 65 years. All patients in the study were commercially insured in a plan that offered prescription coverage and were likely

healthier and younger than the general population of CML patients. However, our findings may well be applicable to CML patients aged 65 years and older despite excluding Medicare beneficiaries, who constitute about half of all patients with CML at diagnosis.²¹

The 5-year study period of 2011-2015 allowed for a good observation of CML patients receiving imatinib, dasatinib, and nilotinib, which were the first 3 TKIs approved by the U.S. Food and Drug Administration (FDA) for CML treatment in 2001, 2006, and 2007, respectively.⁴⁸ This resulted in our study having a negligible number of CML patients on bosutinib and ponatinib—2 TKIs that were approved by the FDA for CML treatment in 2012.⁴⁸ When we excluded these patients from our analysis, we obtained similar findings.

Conclusions

Patients with earlier TKI initiation were at lower risk of adverse events such as hospitalizations, resulting in lower medical costs. These lower costs would partially offset their higher TKI pharmacy costs.

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