Comparative Safety and Health Care Expenditures Among Patients With Chronic Myeloid Leukemia Initiating First-Line Imatinib, Dasatinib, or Nilotinib

Ashley L. Cole, MPH, PhD[1,2]; William A. Wood Jr, MPH, MD[3,4]; Benyam Muluneh, PharmD[5]; Jennifer L. Lund, MSPH, PhD[4,6]; Jennifer Elston Lafata, PhD[1,4]; Stacie B. Dusetzina, PhD[7,8]

QUESTION ASKED: Given that no significant differences in overall survival have been observed in clinical trials, are there differences in safety or cost that could help inform the first-line treatment decision for patients with chronic myeloid leukemia (CML)?

SUMMARY ANSWER: In this study, patients who received imatinib as first-line treatment for CML had the lowest risk of hospitalization or emergency department (ED) visits and 1-year health care expenditures when compared with patients treated with dasatinib and nilotinib.

WHAT WE DID: By using data from commercial and Medicare supplemental insurance claims, we compared the risk of hospitalizations and ED visits (safety events) and 1-year inflation-adjusted all-cause and out-of-pocket health care expenditures between inverse probability of treatment weighted patients with CML who were newly treated with imatinib, dasatinib, or nilotinib as first-line therapy.

WHAT WE FOUND: Over a median of 1.7 years, the cumulative incidence of safety events was higher among patients initiating dasatinib (hazard ratio, 1.23; 95% CI, 1.10 to 1.38) and nilotinib (hazard ratio, 1.08; 95% CI, 0.95 to 1.24) compared with patients initiating imatinib. One-year health care expenditures were high (median, $125,987) and were significantly higher among patients initiating second-generation tyrosine kinase inhibitors (TKIs) compared with imatinib (difference in medians: dasatinib *v* imatinib, $22,393; 95% CI, $17,068 to $27,718; nilotinib *v* imatinib, $19,463; 95% CI, $14,689 to $24,236).

BIAS, CONFOUNDING FACTORS: We used ED visits and hospitalizations as a proxy for safety events (ie, requiring immediate medical attention or inpatient stay), but we cannot be sure that all events were related to treatment with TKIs. Our study sample may have been younger and healthier and may have had better insurance coverage than the general CML population; therefore, true differences may be larger in an older population with a higher comorbidity burden. Although we controlled for hypothesized confounders using inverse probability of treatment weighted patients, we cannot fully rule out residual treatment group differences as a result of unmeasured confounders.

REAL-LIFE IMPLICATIONS: Randomized controlled trials have observed no significant differences in overall survival when comparing dasatinib and nilotinib to imatinib for first-line treatment of CML. Given our findings that imatinib was the safest and least expensive treatment option in a real-world clinical practice setting, imatinib may represent the ideal first-line therapy for patients with CML, on average. However, considerations such as TKI discontinuation and individual-level risk factors for treatment-related adverse events are also important and require future research.

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ASSOCIATED CONTENT

Appendix

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abstract

PURPOSE Tyrosine kinase inhibitors (TKIs) have dramatically improved survival for patients with chronic myeloid leukemia (CML). No overall survival differences were observed between patients initiating first- and second-generation TKIs in trials; however, real-world safety and cost outcomes are unclear. We evaluated comparative safety and health care expenditures between first-line imatinib, dasatinib, and nilotinib among patients with CML.

PATIENTS AND METHODS Eligible patients had one or more fills for imatinib, dasatinib, or nilotinib in the MarketScan Commercial and Medicare Supplemental databases between January 1, 2011, and December 31, 2016 (earliest fill is the index date), 6 months pre-index continuous enrollment, CML diagnosis, and no TKI use in the pre-index period. Hospitalizations or emergency department visits (safety events) were compared across treatment groups using propensity-score-weighted 1-year relative risks (RRs) and subdistribution hazard ratios (HRs). Inflation-adjusted annual health care expenditures were compared using quantile regression.

RESULTS Eligible patients included 1,417 receiving imatinib, 1,067 receiving dasatinib, and 647 receiving nilotinib. The 1-year risk of safety events was high: imatinib, 37%; dasatinib, 44%; and nilotinib, 40%, with higher risks among patients receiving dasatinib (RR, 1.17; 95% CI, 1.06 to 1.30) and nilotinib (RR, 1.07; 95% CI, 0.93 to 1.23) compared with those receiving imatinib. Over a median of 1.7 years, the cumulative incidence of safety events was higher among patients receiving dasatinib (HR, 1.23; 95% CI, 1.10 to 1.38) and nilotinib (HR, 1.08; 95% CI, 0.95 to 1.24) than among those receiving imatinib. One-year health care expenditures were high (median, $125,987) and were significantly higher among patients initiating second-generation TKIs compared with those receiving imatinib (difference in medians: dasatinib *v* imatinib, $22,393; 95% CI, $17,068 to $27,718; nilotinib *v* imatinib, $19,463; 95% CI, $14,689 to $24,236).

CONCLUSION Patients receiving imatinib had the lowest risk of hospitalization or emergency department visits and 1-year health care expenditures. Given a lack of significant differences in overall survival, imatinib may represent the ideal first-line therapy for patients, on average.

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INTRODUCTION

Tyrosine kinase inhibitors (TKIs) have dramatically improved survival for patients with chronic myeloid leukemia (CML).[1] Since the initial approval of imatinib in 2001, several second-generation TKIs have been approved for first-line treatment of CML. Clinical trials comparing dasatinib, nilotinib, and most recently, bosutinib with imatinib have demonstrated faster and deeper molecular responses among patients who received these newer TKIs; however, to date no significant differences in overall survival have been observed between first- and second-generation drugs.[2-4] As a result, treatment guidelines do not specify which of these medications approved by the US Food and Drug Administration (FDA) should be used as first-line therapy.[5,6]

Aside from effectiveness, there are other important considerations in making the initial treatment decision. First, these treatment drugs have distinct safety profiles.[7] Although previous studies have reported on specific types of adverse events, such as vascular events for patients treated with nilotinib and pulmonary events for patients treated with dasatinib, the overall comparative safety in real-world settings remains

unclear.[8-27] Second, health care expenditures in the CML population are also a major concern.[28] Branded TKIs are currently priced at more than $10,000 per month in the United States, and patients typically continue to use these drugs for their entire lives once they have been initiated.[29,30] In addition to the acquisition cost of the TKIs themselves, adverse events can result in costly hospitalizations and emergency department (ED) visits. Comparative health care expenditures for patients who initiate each of the TKIs approved for first-line use is unclear. To address these uncertainties and to inform the decision on initial treatment for patients newly diagnosed with CML, we compared ED and hospitalizations as a proxy for adverse events and health care expenditures among patients initiating imatinib, dasatinib, or nilotinib.

PATIENTS AND METHODS

Using the MarketScan Commercial Claims and Encounters and Medicare Supplemental databases (IBM Watson Health), we identified patients with at least 1 prescription fill for imatinib, nilotinib, or dasatinib between 2011 (the first calendar year during which all three treatments were available as first-line therapy for CML) and 2016 (to allow for 1 year of follow-up). The earliest observed fill was defined as the index date. The study population was restricted to patients with at least 6 months of continuous enrollment before the index date. Patients were excluded if they had a TKI fill in the 6-month pre-index period or if they did not have an inpatient or outpatient medical claim for CML (International Classification of Disease, 9th or 10th Revision, codes 205.1x or C92.10 to C92.12, respectively) during the 6-month baseline period or within 30 days after the index date. Eligible patients were classified into one of three treatment groups on the basis of the first-line therapy they initiated (imatinib, dasatinib, or nilotinib). The subpopulation of patients with at least 1 year of continuous enrollment after the index date was eligible for analysis comparing all-cause health care expenditures.

To evaluate real-world comparative safety, we compared the incidence of hospitalizations or ED visits after TKI initiation using a variable follow-up period beginning with the index date and ending with the end of the patient's continuous enrollment in the health plan. After inverse probability of treatment weighting (IPTW), the 1-year risk, relative risk (RR), and cumulative incidence of a hospitalization or ED visit were estimated by using the subdistribution hazard function. Inpatient death, stem cell transplantation, and TKI switches were treated as competing risks, because these events preclude the occurrence of a treatment-related event. For example, if a patient who initiated imatinib was switched to dasatinib later in the year, only the time before the switch was considered as being at risk for experiencing an event. Patients were censored at the end of continuous enrollment in the health plan.[31,32]

One-year all-cause health care expenditures and out-of-pocket costs recorded on medical and pharmacy claims were measured in the year after treatment initiation for the subset of patients with at least 1 year of follow-up. In addition to summarizing total health care expenditures, we summarized all-cause health care expenditures specific to each of the following categories: inpatient medical, ED, outpatient medical, and outpatient pharmacy. After IPTW, expenditures were compared across treatment groups using quantile regression, which allows for estimation of treatment group differences across the spending distribution. This approach minimizes the effect of outliers and is useful when modeling cost data, which is often highly skewed. In sensitivity analyses, we used more traditional generalized linear modeling (GLM) methods to compare log mean differences across treatment groups. In these models, the modified Park test was used to guide selection of the appropriate distribution.[33] All cost amounts were adjusted for inflation by using the medical care component of the consumer price index.[34]

Because patient-level prognostic characteristics may influence the initial choice of treatment, we used stabilized IPTW to balance treatment groups on potential confounding factors.[35] Weights were estimated as the marginal probability of treatment divided by the patient's predicted probability of the treatment received, given his or her observed characteristics (propensity score).[36] Propensity scores were estimated from a multinomial logistic regression model and included the following dependent variables: age group (< 34, 35-54, 55-64, 65-74, and 75+ years), sex, geographic region (northeast, north central, south, west), payer (commercial or Medicare), type of health plan (comprehensive or indemnity, exclusive provider organization or preferred provider organization, point-of-service, health maintenance organization, consumer-driven or high-deductible health plan), urban or rural residence (urban included patients living in a metropolitan statistical area), index year, average daily dose of index prescription fill (doses above those recommended for chronic phase treatment were used as a proxy for advanced phase CML), prescription drug plan generosity (mean prescription drug cost sharing above or below 20% in the baseline period), baseline non-cancer health care expenditures (total amount paid on all claims without a diagnosis of cancer), hospitalization or ED visit in the baseline period, Klabunde-Charlson comorbidity index[37] (0, 1, 2, 3+), disability status,[38] number of concomitant medications in the baseline period, evidence of smoking,[39] and evidence of overweight or obesity. We also included indicators for comorbidities that may influence treatment choice (eg, trials suggest that nilotinib is associated with an increased risk of vascular occlusive events; therefore, patients with cardiovascular disease may be channeled away from nilotinib in favor of another TKI). The following comorbidities were measured using the Agency for Health Care Research

Clinical Classifications Software: diabetes, vascular comorbidities, cardiac comorbidities, pulmonary comorbidities, liver disease, GI disease, pancreatic disorders, thyroid disorders, and kidney disease.[7,40] Separate propensity score models were fit for the main study population and the subgroup eligible for comparative health care expenditure analysis. Absolute standardized differences of less than 10% across treatment groups were considered adequately balanced.

RESULTS

The final study sample consisted of 1,417 imatinib-treated, 1,067 dasatinib-treated, and 647 nilotinib-treated patients (Table 1). Characteristics of the weighted study population are provided in Table 2. The study sample was 54% male with a median age of 55 years. After weighting, all absolute standardized differences were less than 10%. The weighted sample had a median of 615 days (1.7 years) of follow-up time (25th percentile, 0.80 years; 75th percentile, 3.0 years).

The 1-year risk of hospitalization or ED visit was high across groups (imatinib: 1-year risk, 0.37; 95% CI, 0.35 to 0.40; dasatinib: 1-year risk, 0.40; 95% CI, 0.36 to 0.45; nilotinib: 1-year risk, 0.44; 95% CI, 0.41 to 0.47). The 1-year RR of a hospitalization or ED visit was significantly higher among patients who initiated dasatinib compared with those who initiated imatinib (1-year RR, 1.17; 95% CI, 1.06 to 1.30), and it was higher (although not statistically significant) among patients who initiated nilotinib compared with imatinib (1-year RR, 1.07; 95% CI, 0.93 to 1.23; Table 3). Over the entire follow-up period, the cumulative incidence of a hospitalization or ED visit was higher among patients who initiated dasatinib compared with imatinib (hazard ratio [HR], 1.23; 95% CI, 1.10 to 1.38; Table 3), although the incidence of events among nilotinib-treated patients seemed to increase later in the study period and approached that of dasatinib-treated patients (Fig 1).

Within the larger study sample, 969 imatinib-treated, 708 dasatinib-treated, and 466 nilotinib-treated patients were eligible for the 1-year health care expenditures comparison, and groups were well-balanced on all measured characteristics after weighting (Appendix Table A1, online only). All-cause health care expenditures and patient out-of-pocket costs are presented in Table 4. Total all-cause health care expenditures were high across groups (median, $126,525; interquartile range [IQR], $93,355-$153,646) and were largely driven by outpatient pharmacy spending (median, $105,402; IQR, $74,177-$129,819). In weighted median regression models, patients treated with second-generation TKIs (dasatinib or nilotinib) had significantly higher median all-cause health care expenditures compared with patients who received imatinib (difference in medians: dasatinib *v* imatinib, $22,393; 95% CI, $17,068 to $27,718; nilotinib *v* imatinib, $19,463; 95% CI, $14,689 to $24,236; Table 5).

Although median all-cause health care expenditures were similar between patients who initiated dasatinib and nilotinib, mean all-cause health care expenditures were higher among dasatinib initiators (mean, $158,507; standard deviation, $158,465) compared with nilotinib initiators (mean, $140,049; standard deviation, $103,983). Results of GLM models are included in Appendix Table A2).

One-year median patient out-of-pocket costs were $2,383 across treatment groups (IQR, $1,342-$4,329). Outpatient pharmacy claims made up a large portion of patient out-of-pocket costs, although not to the same extent as all-cause health care expenditures (Table 4). Regression estimates revealed that median patient out-of-pocket costs were significantly higher in the nilotinib cohort compared with the imatinib cohort (difference in medians, $332; 95% CI, $53 to $612; Table 5); however, quantile regression plots revealed that this effect was not consistent across the distribution (Appendix Figures A1-A4).

TABLE 1. Selection of the Study Sample

	Imatinib		Dasatinib		Nilotinib	
Selection Criteria	**No.**	**%**	**No.**	**%**	**No.**	**%**
Patients in MarketScan Commercial and Medicare Supplemental Databases with one or more claims for imatinib, nilotinib, or dasatinib between January 1, 2011, and December 31, 2016 (earliest dispense date is the index date)	9,732	100	2,790	100	1,639	100
No TKI use during the baseline period (new users)	6,859	70	2,416	87	1,358	83
Diagnosis of CML during the 6-month baseline period or 30 days or fewer after the index date[a]	2,818	41	1,705	71	1,108	82
With at least 6 months of continuous enrollment and pharmacy benefits before the index date (main study sample)	1,417	50	1,067	63	647	58
With at least 12 months of continuous enrollment and pharmacy benefits after the index date (health care expenditure analysis subpopulation)	970	68	712	67	464	72

Abbreviations: CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

[a]A higher proportion of imatinib patients had diagnoses for other indications, such as GI stromal tumor.

TABLE 2. Selected Baseline Characteristics of TKI Initiators After Propensity Score Weighting

	Imatinib (n = 1,417)				Dasatinib (n = 1,067)				Nilotinib (n = 647)			
	No.	%	Mean	SD	No.	%	Mean	SD	No.	%	Mean	SD
Age group, years												
< 34	165	11.6			123	11.6			76	11.7		
35-54	524	37.0			391	36.9			231	35.7		
55-64	419	29.6			316	29.8			198	30.6		
65-74	153	10.8			114	10.8			70	10.8		
≥ 75	156	11.0			117	11.0			73	11.3		
Male sex	780	55.0			576	54.3			346	53.4		
Insurance plan type												
Comprehensive/indemnity	170	12.0			122	11.5			79	12.2		
EPO/PPO	804	56.7			604	57.0			374	57.6		
POS/POS with capitation	104	7.3			80	7.5			47	7.3		
HMO	164	11.6			123	11.6			73	11.2		
CDHP/HDHP	125	8.8			93	8.8			54	8.4		
Unknown	52	3.6			38	3.6			22	3.3		
Commercial payer	1,099	77.5			824	77.6			500	77.2		
Lives in an MSA	1,212	85.5			904	85.2			554	85.5		
Index dose for advanced disease	119	8.4			80	7.6			54	8.3		
< 20% prescription drug cost sharing	805	56.8			602	56.7			367	56.7		
Any hospitalization	398	28.1			299	28.2			190	29.3		
Any ED visit	385	27.2			293	27.6			175	27.1		
Total non-cancer expenditures ($)			8,835	14,584			9,334	17,924			8,501	14,875
Klabunde-Charlson comorbidity index			0.6	1.2			0.6	1.1			0.6	1.2
Poor Davidoff disability status	39	2.7			35	3.3			20	3.1		
No. of unique medications			6.8	5.8			6.8	5.6			6.5	5.2
Comorbidities present in 5% or more of patients[a]												
Diabetes	187	13.2			140	13.2			81	12.6		
Vascular conditions	457	32.2			346	32.6			205	31.7		
Cardiac conditions	187	13.2			138	13.0			83	12.9		
Pulmonary conditions	104	7.3			73	6.9			53	8.2		
Thyroid disorders	81	5.7			65	6.1			39	6.0		
Kidney disease	81	5.7			55	5.2			37	5.6		

Abbreviations: CDHP, consumer-driven health plan; ED, emergency department; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; MSA, metropolitan statistical area; POS, point of service; PPO, preferred provider organization; SD, standard deviation; TKI, tyrosine kinase inhibitor.

[a]Comorbidity categories are not mutually exclusive; therefore, patients may be represented in more than one category.

DISCUSSION

Life expectancy for CML patients is now approaching that of the general population, and several TKIs have been approved for first-line therapy.[1,41] Given that most patients receive lifelong treatment, tolerability and cost of care are important concerns that should be considered in the initial treatment decision. To that end, this study compared the 1-year incidence of safety events (measured as hospitalizations and ED visits), all-cause health care expenditures, and patient out-of-pocket costs across patients with CML who initiated treatment with imatinib, dasatinib, or nilotinib.

Overall, we observed that, after accounting for baseline differences across treatment groups, patients who initiated first-line imatinib had the lowest incidence of safety events and the lowest all-cause health care expenditures compared with patients who initiated first-line treatment with a second-generation TKI. Given that no significant differences in overall survival have been observed among clinical

TABLE 3. Weighted Occurrence of Any Hospitalization or ED Visit After Initiation of First-Line Imatinib, Dasatinib, or Nilotinib

Index TKI	1-Year Risk	95% CI	1-Year RR	95% CI	HR	95% CI[a]
Imatinib	0.37	0.35 to 0.40	1.00 (ref)		1.00 (ref)	
Dasatinib	0.40	0.36 to 0.45	**1.17**	**1.06 to 1.30**	**1.23**	**1.10 to 1.38**
Nilotinib	0.44	0.41 to 0.47	1.07	0.93 to 1.23	1.08	0.95 to 1.24

NOTE. Statistically significant estimates are shown in bold.

Abbreviations: ED, emergency department; HR, hazard ratio; ref, reference; RR, relative risk; TKI, tyrosine kinase inhibitor.

[a]For the HR, patients were censored at the end of continuous enrollment in the health plan, with variable follow-up time (not restricted to 1 year).

trial patients, this evidence supports imatinib as the preferred first-line treatment of most patients.[2-4]

In addition to observing relative differences in the occurrence of safety events, we also observed that the 1-year risk of a safety events was high across treatment groups, which highlights the importance of future research aimed at reducing this burden. Given that TKIs have numerous potential adverse events that vary widely across treatments, this may include the development of treatment selection tools that tailor the first-line treatment choice based on a patient's comorbidities and/or risk factors for treatment-specific adverse events. Although trials suggest that most adverse events will occur within the first year after treatment is initiated, some more clinically serious events, such as vascular occlusive events associated with the use of nilotinib, may have a longer time to onset. The median follow-up time in our study was 1.7 years, which limits our ability to detect significant differences between treatment groups for events that occur farther out from treatment initiation. In survival curves, the cumulative incidence of safety events among nilotinib-treated patients seemed to increase later in the follow-up period, highlighting the need for future studies with longer follow-up to fully understand the comparative safety of these products.

Although lifelong TKI use has historically been the standard of care for patients with CML, the possibility of discontinuation for patients who achieve and maintain a deep molecular response is supported by the most recent CML treatment guidelines.[5] Nilotinib recently became the first TKI to obtain FDA approval for discontinuation.[42,43] For patients who are able to maintain treatment-free remission after initial nilotinib therapy, late effects such as vascular occlusive events may be less of a concern. However, difficulty prospectively identifying candidates for discontinuation at the time of the initial treatment decision may make this strategy difficult to implement in clinical practice.[44] Furthermore, it is worth noting that the largest study of TKI discontinuation to date observed no significant differences in molecular relapse-free survival among patients who received first-line imatinib, dasatinib, or nilotinib.[45] Although the median duration of TKI exposure was shorter for patients who received first-line nilotinib in the ENESTFreedom trial (ClinicalTrials.gov identifier: NCT01784068) compared with studies of imatinib discontinuation (approximately 5 years *v*6 to 9 years), the substantially reduced price of generic imatinib combined with potentially better tolerability may outweigh a longer first-line treatment duration.[43,46,47] Although it is unlikely that manufacturers will pursue FDA approval for imatinib discontinuation, given that it is now off patent, this tradeoff is an important area for future research.

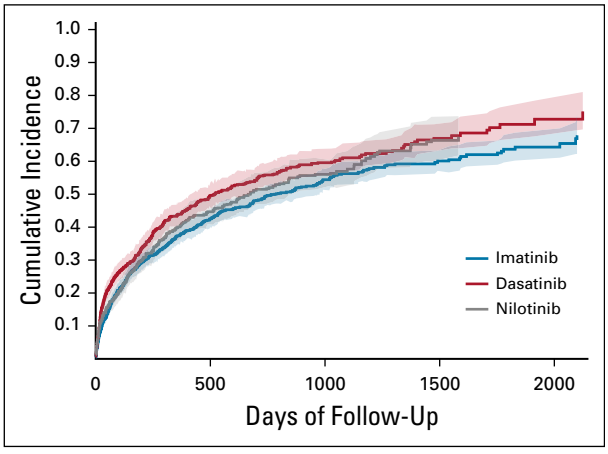

FIG 1. Weighted cumulative incidence of any hospitalization or emergency department visit following initiation of first-line imatinib, dasatinib, or nilotinib. Shaded areas represent 95% CIs.

With respect to all-cause health care expenditures, we observed that most health care expenditures and out-of-pocket expenses occurred in the outpatient pharmacy setting. This is not surprising, given the high price of TKIs, which has been the subject of discussion in the CML community. However, even after excluding outpatient pharmacy expenditures, median 1-year medical expenditures were higher among patients who initiated first-line nilotinib or dasatinib, perhaps partly reflecting the increased incidence of hospitalizations and ED visits observed in safety comparisons.

Notably, generic imatinib has been available in the United States since February 2016, substantially reducing the list price for payers compared with the prices for dasatinib and nilotinib (as of this writing, monthly list prices for chronic CML dosing of imatinib start at roughly $600 compared with approximately $13,800 for dasatinib and $13,600 for nilotinib).[48-50] Given that generic imatinib is chemically equivalent to the branded product, we would expect no differences in the incidence of safety events between

TABLE 4. Weighted Mean and Median All-Cause Health Care Expenditures and Patient Out-of-Pocket Costs in the Year After Initiation of First-Line Imatinib, Dasatinib, or Nilotinib

	Imatinib (n = 970)				Dasatinib (n = 712)				Nilotinib (n = 464)			
	Mean	SD	Median	IQR	Mean	SD	Median	IQR	Mean	SD	Median	IQR
Total health care expenditures	131,236	106,212	114,843	55,263	158,507	158,465	137,235	58,425	140,049	103,983	134,306	55,213
Medical expenditures[a]	36,076	101,009	9,561	20,445	52,845	157,069	11,438	21,767	35,920	101,932	11,484	19,994
Inpatient medical	17,368	77,285	0	0	24,254	114,868	0	475	12,318	60,276	0	0
Emergency department	728	2,164	0	509	732	2,022	0	603	865	3,361	0	499
Outpatient medical	17,980	36,097	8,001	13,090	27,859	67,116	9,657	16,405	22,737	61,095	8,821	12,205
Outpatient pharmacy expenditures	95,160	39,788	95,250	48,695	105,662	42,324	116,226	57,418	104,129	41,029	115,823	59,434
Total patient out-of-pocket costs	3,394	3,849	2,277	2,803	3,668	4,871	2,375	3,045	3,675	4,751	2,609	3,088
Medical out-of-pocket costs[a]	1,546	1,782	988	1,491	1,693	1,749	1,158	1,645	1,553	1,604	1,123	1,533
Inpatient medical	209	993	0	0	185	681	0	0	188	779	0	0
Emergency department	71	266	0	0	69	243	0	6	54	173	0	0
Outpatient medical	1,266	1,305	861	1,219	1,439	1,430	994	1,431	1,311	1,335	962	1,206
Outpatient pharmacy out-of-pocket costs	1,848	3,327	888	1,245	1,975	4,483	883	1,416	2,122	4,388	1,051	1,461

NOTE. All costs/expenditures are in US $.

Abbreviations: IQR, interquartile range; SD, standard deviation; TKI, tyrosine kinase inhibitor.

[a]Includes payments found on inpatient and outpatient medical claims (including physician-administered prescription drugs).

patients who initiate branded versus those who initiated generic imatinib. In fact, generic imatinib may produce better outcomes than branded imatinib if price decreases for payers translate into lower costs for patients and improved patient uptake and medication adherence.

Patients' total out-of-pocket costs were considerable, with more than half of patients paying more than $2,000 out-of-pocket in the year after treatment initiation, but they remained low relative to total health care expenditures. This is likely a reflection of more generous pharmacy cost-sharing benefits among our employer-insured study population and may not be generalizable to Medicare beneficiaries or uninsured patients with CML. Like all-cause health care expenditures, because generic medications typically receive preferential formulary placement, availability of generic imatinib may result in additional decreases in patient out-of-pocket costs.

This study has important limitations. We relied on health insurance claims to identify patients who used TKIs and their outcomes; these data are not collected for research purposes. Our reliance on hospitalizations and ED visits as a proxy for safety events yielded an imperfect assessment of the comparative safety of these treatments. However, given that serious adverse events include those that result in hospitalization and/or require immediate medical attention, these events are clinically important. In addition, we cannot be sure that the hospitalizations and ED visits we observed were related to treatment with TKIs; however, we used IPTW to balance treatment groups on potential confounding factors (including risk factors for treatment-specific adverse events) in an attempt to isolate treatment-outcome associations. Because of the relative size differences between commercially insured and Medicare-insured groups of individuals in the MarketScan databases, our population of patients with CML may be younger and healthier and may have better insurance coverage than the general CML population. As a result, differences among treatment groups observed here may be smaller than would be observed in an older population with a higher comorbidity burden; this is an important area for future research. Prescription drug expenditure amounts included in administrative claims

TABLE 5. Median Regression Estimates for Differences in All-Cause Health Care Expenditures and Patient Out-of-Pocket Costs in the Year Following Initiation of First-Line Imatinib, Dasatinib, or Nilotinib Among Patients with CML

	1-Year All-Cause Health Care Expenditures ($)		1-Year Patient Out-of-Pocket Costs ($)	
Index TKI	Effect	95% CI	Effect	95% CI
Imatinib	0 (ref)		0 (ref)	
Dasatinib	**22,393**	**17,068 to 27,718**	98	–206 to 403
Nilotinib	**19,463**	**14,689 to 24,236**	**332**	**53 to 612**

NOTE. Statistically significant estimates are shown in bold.

Abbreviations: CML, chronic myeloid leukemia; ref, reference; TKI, tyrosine kinase inhibitor.

data represent point-of-sale prices and do not account for post-sale rebates or volume-based discounts received by health plans from manufacturers of branded drugs, which can be substantial and vary widely across products. As a result, true differences observed between treatment groups in all-cause outpatient pharmacy expenditures may be smaller than those we observed in this analysis. However, rebates for branded second-generation TKIs are unlikely to result in net prices lower than that for generic imatinib, based on current pricing. Furthermore, many branded products offer coupons for commercially insured patients that lower their out-of-pocket spending. This may offset costs to patients for use of branded drugs compared with generics, particularly if their benefit structure requires high out-of-pocket costs for generic imatinib. Finally, data were not available for patients initiating first-line bosutinib at the time of this study. Although the price of bosutinib (approximately $14,800 as of this writing) is unlikely to be competitive with generic imatinib, the comparative safety and all-cause health care expenditures for this cohort remain an important area for future research.[51]

Given a lower incidence of hospitalizations and ED visits and lower all-cause health care expenditures, our results suggest that, on average, imatinib may be the preferred first-line option for patients with CML compared with dasatinib and nilotinib. However, considerations such as TKI discontinuation and individual-level risk factors for treatment-related adverse events are also important and warrant future research.

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Disclosures provided by the authors and data availability statement (if applicable) are available with this article at DOI https://doi.org/10.1200/JOP.19.00301.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Comparative Safety and Health Care Expenditures Among Patients With Chronic Myeloid Leukemia Initiating First-Line Imatinib, Dasatinib, or Nilotinib

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APPENDIX

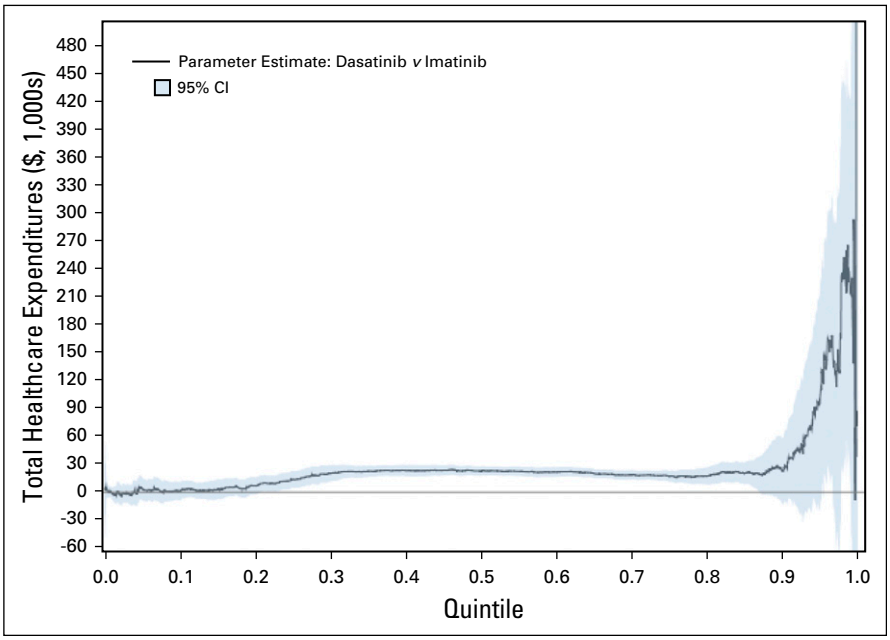

FIG A1. Parameter estimates and 95% CIs across quintiles for weighted differences in total healthcare expenditures in the year following initiation of imatinib or dasatinib.

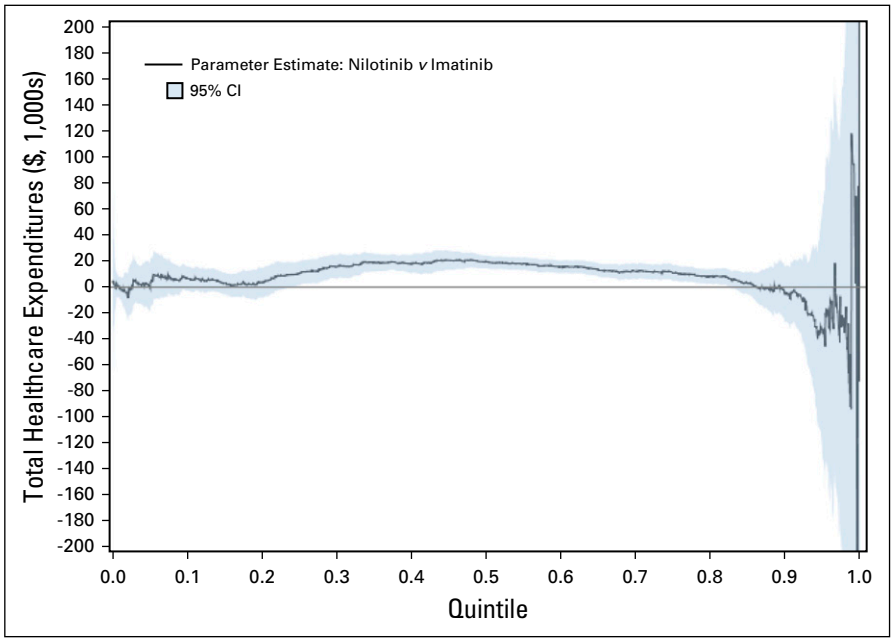

FIG A2. Parameter estimates and 95% CIs across quintiles for weighted differences in total healthcare expenditures in the year following initiation of imatinib or nilotinib.

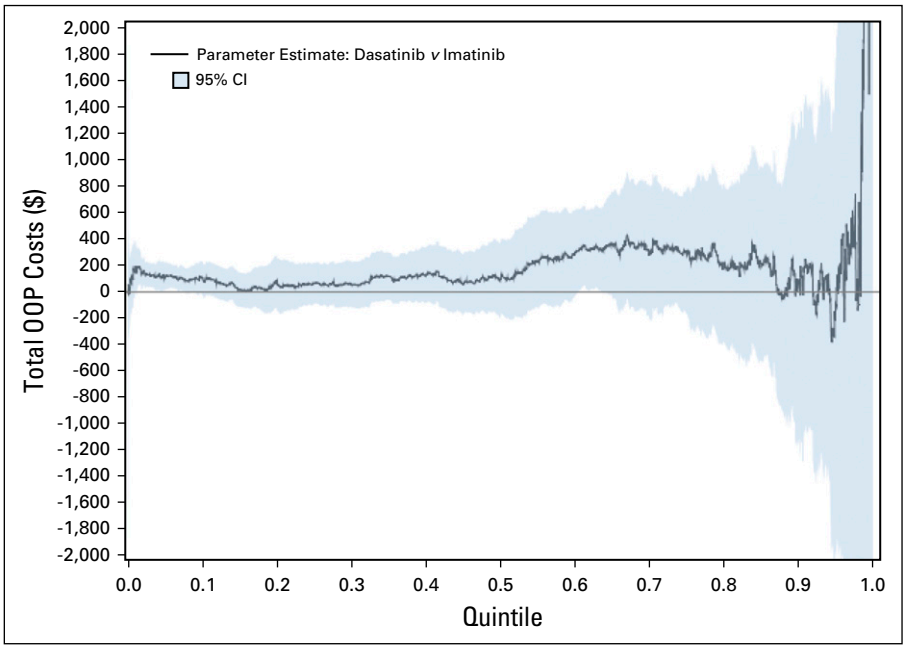

FIG A3. Parameter estimates and 95% CIs across quantiles for weighted differences in out-of-pocket (OOP) healthcare costs in the year following initiation of imatinib or dasatinib.

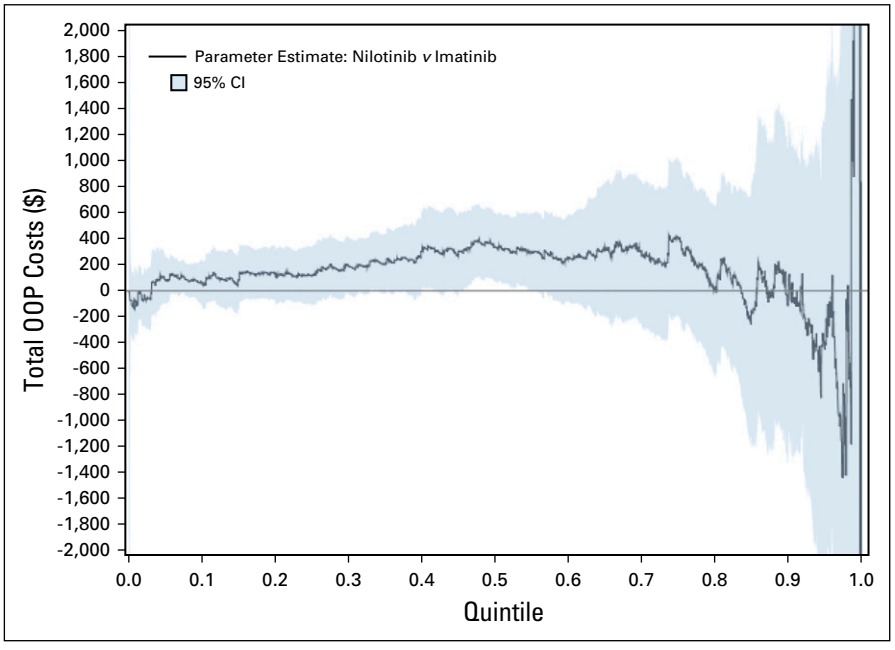

FIG A4. Parameter estimates and 95% CIs across quantiles for weighted differences in out-of-pocket (OOP) healthcare costs in the year following initiation of imatinib or nilotinib.

TABLE A1. Selected Baseline Characteristics of TKI Initiators After Propensity Score Weighting (subpopulation with 1 year of continuous enrollment after TKI initiation)

	Imatinib (N = 970)		Dasatinib (N = 712)		Nilotinib (N = 464)	
Demographic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Age group, years						
< 34	107	11.1	78	11.0	52	11.3
35-54	364	37.6	267	37.7	168	36.1
55-64	284	29.3	209	29.6	146	31.3
65-74	104	10.7	73	10.3	48	10.4
≥ 75	109	11.3	80	11.4	51	11.0
Male sex	529	54.6	378	53.4	254	54.4
Insurance plan type						
Comprehensive/indemnity	125	12.9	89	12.6	57	12.2
EPO/PPO	550	56.7	403	57.0	269	57.8
POS/POS with capitation	73	7.5	54	7.7	39	8.3
HMO	115	11.9	82	11.6	52	11.2
CDHP/HDHP	84	8.7	63	8.8	39	8.3
Unknown	23	2.4	17	2.4	10	2.2
Commercial payer	746	76.9	548	77.5	361	77.5
Lives in an MSA	828	85.5	603	85.2	395	84.8
Index dose for advanced disease	78	8.0	52	7.3	36	7.8
< 20 prescription drug cost sharing	567	58.5	416	58.8	270	57.9
Any hospitalization	265	27.4	200	28.3	133	28.6
Any ED visit	258	26.6	192	27.1	119	25.5
Total non-cancer expenditures, $ (mean, SD)	8,435	14,195	8,765	15,241	8,622	14,822
Klabunde-Charlson Comorbidity Index (mean, SD)	0.6	1.0	0.6	1.1	0.6	1.1
Poor Davidoff Disability status	24	2.5	21	3.0	12	2.6
Number of unique medications (mean, SD)	6.7	5.6	6.7	5.4	6.6	5.1
Comorbidities present in ≥ 5 of patients						
Diabetes	114	11.7	96	13.6	56	12.1
Vascular conditions	305	31.5	226	31.9	143	30.6
Cardiac conditions	128	13.2	73	10.4	50	10.7
Pulmonary conditions	75	7.8	48	6.8	30	6.5
Thyroid disorders	63	6.5	45	6.4	21	4.5
Kidney disease	54	5.5	37	5.2	31	6.6

Abbreviations: CDHP, consumer-driven health plan; ED, emergency department; EPO, exclusive provider organization; HDHP, high deductible health plan; HMO, health maintenance organization; MSA, metropolitan statistical area; POS, point of service; PPO, preferred provider organization; SD, standard deviation; TKI, tyrosine kinase inhibitor.

TABLE A2. Weighted Generalized Linear Model Results for Differences in All-Cause Healthcare Expenditures and Patient Out-of-Pocket Costs in the Year Following Initiation of Imatinib, Dasatinib, or Nilotinib

Index TKI	All-Cause Healthcare Expenditures, Effect (95% CI)	Patient Out-of-Pocket Costs, Effect (95% CI)
Imatinib	1.00 (reference)	1.00 (reference)
Dasatinib	**1.21 (1.10 to 1.33)**	1.08 (0.96 to 1.22)
Nilotinib	1.07 (0.97 to 1.17)	1.08 (0.92 to 1.27)

NOTE. Statistically significant estimates are shown in bold.
Abbreviation: TKI, tyrosine kinase inhibitor.