Adherence and Persistence Among Chronic Myeloid Leukemia Patients During Second-Line Tyrosine Kinase Inhibitor Treatment

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ABSTRACT

BACKGROUND: Chronic myeloid leukemia (CML) treatment is lifelong, and while it is important for patients to remain adherent to treatment, there are conflicting findings with respect to differences in adherence and persistence with dasatinib or nilotinib during second-line treatment.

OBJECTIVE: To compare the rates of adherence, persistence, and discontinuation of 2 oral second-generation tyrosine kinase inhibitors (TKI), dasatinib and nilotinib, in CML patients during their first 12 months of second-line treatment.

METHODS: Adult CML patients (ICD-9-CM: 205.1x) with 2 consecutive dasatinib or nilotinib prescription claims within 12 months were identified from the Truven Health MarketScan Databases (January 1, 2006-September 30, 2011). Patients were excluded if they had FDA-approved non-CML indications for imatinib, had <6 months continuous enrollment, or had a stem cell/bone marrow transplant in the 6 months pre-index. Patients were followed until the first occurrence of index TKI discontinuation/switch; enrollment end; December 31, 2011; or 12 months follow-up post-index. Index treatment (dasatinib ≤100 mg or nilotinib) was categorized as second-line if there was evidence of only 1 alternative TKI exposure (e.g., imatinib, dasatinib, or nilotinib) anytime during the patient's available claims history. When comparing adherence, persistence, and discontinuation, inverse probability treatment weighting (IPTW) was used. Adherence and persistence measures were calculated as specified by the International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Special Interest Group. Treatment adherence was calculated using medication possession ratio (MPR) and was reported as both continuous and binary measures (i.e., high adherence = MPR ≥ 85%). Persistence was reported as the proportion of days covered (PDC) and estimated level of persistence (ELPT). Finally, discontinuation was defined as a treatment gap of >90 days and absence of index TKI during the remainder of the follow-up period. Time to discontinuation and high adherence of index TKI were compared using weighted Cox proportional hazards and logistic regression models, respectively.

RESULTS: After propensity weighting, the 219 second-line dasatinib patients and the 158 second-line nilotinib patients were similar in mean age, gender, cancer complexity, and comorbidity burden at baseline. Age as a categorical measure, population density, and index year remained imbalanced and were, therefore, included as covariates in the multivariate analysis of adherence. In the bivariate analyses, mean MPR (88.2% vs. 84.4%, $P=0.036$); proportion of patients with high adherence (72.7% vs. 63.3%, $P=0.006$); and ELPT (70.4% vs. 62.7%, $P=0.026$) were significantly higher among dasatinib patients than nilotinib patients. Mean PDC was not significantly different between dasatinib and nilotinib patients (0.79 vs. 0.77, $P=0.328$) after propensity weighting. In addition, a significantly lower proportion of second-line dasatinib patients discontinued their index therapy compared with second-line nilotinib patients (4.4% vs. 8.6%, $P=0.020$). With a hazard ratio (HR) of 0.50 (95% CI = 0.27-0.93, $P=0.029$), dasatinib patients had half the possibility of discontinuing treatment compared with nilotinib patients at any point in time. After accounting for the baseline factors remaining imbalanced and controlling for cancer complexity and number of concomitant medications at baseline, second-line dasatinib patients were 1.7 times (95% CI = 1.2-2.4) more likely to be highly adherent than second-line nilotinib patients ($P=0.0016$).

CONCLUSIONS: Among second-line TKI-treated CML patients, dasatinib patients had significantly higher adherence and lower discontinuation rates compared with patients receiving second-line nilotinib.

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What is already known about this subject

- Chronic myeloid leukemia (CML) treatment is lifelong; it is important for patients to remain adherent to treatment.
- Conflicting findings with respect to differences in adherence and persistence with dasatinib or nilotinib during second-line treatment have been found.

What this study adds

- CML patients treated with dasatinib at the currently prescribed daily dose of ≤100 mg were found to be significantly more adherent and persistent to therapy during second-line treatment than those treated with nilotinib, and the proportion of patients discontinuing second-line nilotinib was twice that of second-line dasatinib.
- As additional tyrosine kinase inhibitors are approved for the treatment of CML, it is increasingly important to understand patients' medication-taking behaviors, such as adherence to treatment, since treatment is strongly associated with positive clinical outcomes.

Chronic myeloid leukemia (CML) is a bone marrow and blood disorder accounting for 15% of adult leukemias.[1] CML is associated with a chromosomal abnormality where there is a translocation of chromosomes 9 and 22, which code for the BCR-ABL tyrosine kinase. The American Cancer Society estimates there will be 5,980 new cases of CML diagnosed (3,130 in men and 2,850 in women) during 2014 and 810 people will die of CML during this same time period.[2] The median age at onset is 67 years, but CML occurs in all age groups.

The 5-year survival rates for CML have increased dramatically with improved treatments, from 31% between 1990 and 1992

to 56% for those diagnosed between 2002 and 2008.[2] In 2001, imatinib became the first therapy approved by the U.S. Food and Drug Administration (FDA) specifically targeting the BCR-ABL protein.[4] In a large study of imatinib, 89% of newly diagnosed CML patients were still alive 5 years after starting treatment.[4]

The FDA approved the following BCR-ABL inhibitors, also known as tyrosine kinase inhibitors (TKIs), for second-line treatment in patients who were resistant to or intolerant of imatinib; dasatinib (Sprycel) 70 milligrams (mg) twice daily (140 mg daily dose) in 2006 and nilotinib (Tasigna) 400 mg (2 × 200 mg) in 2007. A new dasatinib dosing regimen (100 mg once daily) for patients with chronic phase (CP) CML who were resistant or intolerant to prior therapy was later approved in 2007.

Because CML treatment is lifelong, it is important for patients to remain adherent to treatment.[5] Correlations between poor adherence to imatinib therapy and reduced failure-free survival and increased health care costs have been demonstrated among CML patients in clinical and real-world settings.[6-10] Studies of patients treated in the first-line setting with imatinib report highly disparate adherence results ranging from 14% to 98%.[6-9] Recent studies comparing adherence to second-line CML treatment with dasatinib and nilotinib report conflicting results even when the same databases were used for analysis.[9,11,12]

As additional TKIs are approved, it is increasingly important to measure and understand adherence to these treatments so that appropriate measures can be taken in clinical practice to address the issue.[5] The objectives of this study were to compare the rates of adherence, persistence, and discontinuation of the oral TKIs dasatinib (≤ 100 mg) and nilotinib among second-line CML patients using recognized, published methods.[13,14]

Methods

Data Sources

Study data were extracted from the Truven Health MarketScan Commercial and Medicare Supplemental Databases for the time period from January 1, 2006, to December 31, 2011. The databases contain enrollment information and fully adjudicated inpatient medical, outpatient medical, and outpatient pharmacy claims for a large convenience sample of individuals with employer-sponsored primary or Medicare supplemental health insurance. The study databases contained data for over 40 million unique individuals in 2011, enrolled in over 100 health plans across the continuum of managed care. All MarketScan databases are de-identified and fully compliant with U.S. patient confidentiality requirements, including the Health Insurance Portability and Accountability Act (HIPAA) of 1996. The databases have been evaluated and certified by an independent third party to be in compliance with the HIPAA statistical de-identification standards and satisfy the conditions set forth in Sections 164.514 (a)-(b)1ii of the HIPAA privacy rule regarding the determination and documentation of statistically de-identified data.

Subject Selection

Patients were included in the analysis if they met all of the following selection criteria: (a) at least 1 nondiagnostic inpatient or outpatient claim with an *International Classification of Diseases, Ninth Revision, Clinical Modification* (ICD-9-CM) code for CML (205.1x) and at least 2 consecutive prescription claims for the same TKI (dasatinib or nilotinib) within 12 months of each other, between July 1, 2006, and September 30, 2011 (first fill date = index date); (b) aged 18 years or older on the index date; (c) continuously enrolled for at least 6 months pre-index and up to a maximum of 12 months post-index; (d) used only 1 alternative TKI sometime between May 1, 2001 (the launch date of imatinib in the United States) and the day prior to their index date, without a prescription for the index TKI during that same time period (patients with 2 or more alternative TKI agents in the pre-period were excluded); (e) had no bone marrow or stem cell transplant during the pre-index period (see Appendix, available in online article); and (f) had no inpatient or outpatient medical claims with a diagnosis code consistent with any of the following additional labeled indications for imatinib (see Appendix in online article for codes):

- Adult patients with relapsed or refractory Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph + ALL)
- Adult patients with myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements
- Adult patients with aggressive systemic mastocytosis (ASM) without the D816V c-KIT mutation or c-KIT mutational status unknown
- Adult patients with hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown
- Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP)
- Patients with KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)

In May 2007, the labeled dosing of dasatinib for CP CML was changed to 100 mg once daily from the previous 70 mg twice daily (140 mg daily dose). Therefore, to reflect current prescribing practices, 2 second-line treatment cohorts were measured and analyzed: dasatinib (Sprycel) ≤ 100 mg and nilotinib (Tasigna) 400 mg. For several sensitivity analyses, only 1 prescription fill for the index TKI was required.

Study Period

There was a variable-length pre-index period (May 1, 2001, to the day before the index date) to check for the presence or absence of prior TKI use and first CML diagnosis date. For other variables measured prior to index, a fixed period of 6 months ending on the day before index was used. Patients were followed for a maximum of 12 months from their index dates. Patients

were censored based on whichever date came first for the following events: end of follow-up or study period (December 31, 2011), end of enrollment, switch from index treatment, bone marrow or stem cell transplant, or discontinuation.

Demographic and Clinical Characteristics

Patient characteristics evaluated are listed and defined in the Appendix (available in online article). Demographic characteristics were reported as of the index date and included age, gender, geographic region, and health plan type. Clinical characteristics included CML and TKI histories, which were identified using all available medical and prescription claims for study patients from January 2001 to the day prior to the index date. Histories of comorbidities and medication use were evaluated in the 6-month pre-index period. Both the number and type of other chronic conditions and the number of other prescription medications taken were captured, as these may adversely impact adherence to second-line TKI therapies. In addition, the Deyo-Charlson Comorbidity Index was included as a measure of comorbidity burden.[15]

Patients in more advanced stages of CML may have different adherence rates than patients in less advanced stages. Therefore, it is important to adjust for the clinical challenges posed by CML patients with more advanced stages of the disease. However, phase of CML (chronic phase, accelerated phase, or blast crisis) is not identifiable in claims data. Patients were therefore assigned to a cancer complexity index (Darkow et al. 2007[8]). The underlying basis of this measure is that patients with certain diagnoses, associated complications, and adverse events of associated treatments are more difficult to clinically manage. Patients were classified as having either "moderate" or "high" complexity if at least 1 of the diagnoses referenced in the Appendix (available in online article) was present during the 6-month pre-index period. If none were present, the patient was considered to have "usual" complexity.

Inverse Probability Treatment Weights

In order to reduce the impact of bias due to imbalances in baseline demographic characteristics and clinical histories between the treatment cohorts, inverse probability treatment weighting (IPTW) was utilized for outcomes comparisons.[16,17] In this method, the predicted probability of treatment (dasatinib or nilotinib) was determined from logistic regression of treatment as the dependent variable with baseline patient characteristics (see Appendix, available in online article) as the predictors. This probability, known as the propensity score, was determined for each patient. Each individual study patient was then assigned a weight that was the inverse of the individual propensity score. Studies have shown that propensity score matching and IPTW remove systematic differences between subjects in different treatment groups to a greater degree than propensity score stratification or covariate adjustment using the propensity score.[18,19] One particular study showed that IPTW performed better than propensity score matching with sample sizes as low as 60. In light of this evidence and in order to retain the original sample, IPTW was utilized, rather than propensity score matching.[19]

Outcome Measures

Adherence, persistence, and discontinuation of index treatment over the first 12 months following initiation of index treatment were measured. Measurements utilized the fill dates and days' supply information present on retail and mail order prescription claims. Adherence and persistence measures conform to the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Medication Compliance and Persistence Special Interest Group recommendations for measuring these outcomes using retrospective health care claims data.[13,14]

Adherence. Adherence was measured using medication possession ratio (MPR), which is the ratio of the total days' supply of the index TKI across all prescription fills during the refill interval to the total number of days in that interval. The number of days in the refill interval was defined as the number of days between the index date and last prescription fill date of the index TKI prior to the end of the follow-up period plus the days' supply of the last fill. Since patients can refill prescriptions early, it is possible for the calculated MPR to exceed 100%. According to previous cancer research, an MPR of 85% was considered a midpoint threshold.[9] Therefore, adherence was analyzed as a binary outcome, with an MPR ≥ 85% defined as high adherence and <85% as low adherence.

Persistence. Persistence was measured using the proportion of days covered (PDC) and the estimated level of persistence (ELPT). PDC is the ratio of days in possession of the index TKI during the patient's follow-up period to the total number of days of follow-up. When a patient was observed to refill a prescription early, it was assumed that the patient still continued to make use of the days' supply remaining from the prior prescription rather than discarding it. Therefore, the days' supply received at refill was assumed to start on the day after the patient's existing supply ran out. If the days' supply of the last prescription fill extended beyond a patient's end date of follow-up, the days' supply was truncated as of their last day of follow-up. PDC thus cannot exceed 100%.

ELPT is a binary measure that allows for the determination of the percentage of individuals remaining on therapy (persistent) at a given time. During their follow-up periods, if patients consistently refilled each prescription for their index TKIs within a time span of 1.5 times the days' supply of the prior prescription fill, they were considered to be persistent and have no treatment interruption. If they did not refill consistently within the allowed time span, then they were considered to have a treatment interruption. For example, if a patient filled a prescription for a 30-day supply of the index TKI, then the next fill must occur within 45 days of the fill date for the prior prescription to be persistent. If the subsequent fill occurred more than 45 days after the first, then a treatment interruption

is considered to have occurred. A sensitivity analysis was performed where the allowed time span between each refill was 2 times the days' supply of the prior prescription fill.

Discontinuation. Discontinuation was defined to have occurred when a gap in possession of the index TKI of 90 days or longer was observed with no further prescription fills for the index TKI during the remainder of the patient's follow-up period. The end of follow-up was then reset to 90 days after the last date that the patient was in possession of the index TKI. Discontinuation was evaluated as a binary outcome (proportion of patients who discontinued at any time during their follow-up periods). Time to discontinuation was measured as the number of days from the index date to end of follow-up among patients who discontinued. A sensitivity analysis was performed for the comparison of the proportion of patients discontinuing their index TKIs, where discontinuation was redefined as a gap of 60 days or more with no further prescription fills for the index TKI during the remainder of each patient's follow-up period. In addition, using the 90-day gap definition of discontinuation, sensitivity analyses were performed using the larger cohorts of patients where only 1 prescription for the index TKI was required (rather than 2 as was the case for the main study cohorts).

Statistical Analyses. Statistical comparisons of baseline demographic and clinical characteristics across treatment groups were conducted before and after propensity weight adjustment. Outcomes were compared only after propensity weight adjustment. Student t-tests or Wilcoxon rank-sum tests were utilized to test for statistically significant differences in continuous measures, while chi-square or Fisher's exact tests were used for categorical measures, depending on the distributional properties of each measure. Where imbalance (i.e., statistically significant differences $P<0.05$) remained between the treatment cohorts after accounting for the patient weights in any demographic or clinical characteristics used in the development of the IPTWs, the measure was included as a covariate in all outcome regression models.

Logistic regression of high adherence (MPR ≥ 85%) and a Cox proportional hazards model of time to discontinuation to compare dasatinib and nilotinib were run utilizing the IPTWs. Covariates for both models included patient characteristics that remained imbalanced after propensity score weighting. Since comorbidity and prescription medication burdens have been shown to be associated with medication adherence overall, and in CML treatment with imatinib specifically, cancer complexity—as a proxy for disease severity—and number of preperiod prescription therapy classes were included as predictors in the model of high adherence.[5,9,20] Odds ratios (OR) and their 95% confidence intervals (CI) are presented for all the covariates included in the logistic regression model. The HR and 95% CI for index TKI is presented for the Cox regression.

All statistical analyses were conducted using SAS version 9.3 for PC (SAS Institute, Inc., Cary, NC). All tests were two-sided and evaluated at $P<0.05$.

Results

Sample Selection

In the study databases, there were 23,392 patients with a diagnosis of CML on a nondiagnostic medical claim between January 1, 2001, and September 30, 2011. Among those, there were 219 patients with an index TKI of dasatinib ≤ 100 mg and 158 patients with an index TKI of nilotinib who had 2 consecutive prescription fills for their index TKIs and met all of other the inclusion and exclusion criteria for the study. Figure 1 presents detailed information on patient attrition at each step in the sample selection process. When the requirement of 2 consecutive prescription fills for the index TKI was relaxed to require only 1 prescription fill for inclusion in 1 of the discontinuation sensitivity analyses, an additional 57 dasatinib ≤ 100 mg patients and 42 nilotinib patients were available.

Patient Characteristics

Overall, the average age of study patients (n = 377) was 54.6 (standard deviation [SD] 15.3) years, and 52.8% were male. Although age as a continuous measure was included in the determination of the IPTWs, age cohort remained imbalanced after the IPTW was performed (Table 1; $P=0.038$). Thus, age cohort and population density, which also remained imbalanced between the study cohorts (Table 1), were the only demographic variables included as covariates in the regression models for adherence and time to discontinuation.

Of all the comorbidities evaluated in the pre-index period, only ischemic heart disease differed among the cohorts, and only after accounting for the patient weights (dasatinib 5.9% vs. nilotinib 2.9%, $P=0.116$ before and dasatinib 5.7% vs. nilotinib 2.5%, $P=0.029$ after). There were no other significant differences in comorbidities. The majority of patients (71.1%) had usual cancer complexity in the pre-index period, with fewer patients having moderate (18.0%) and high (10.9%) cancer complexity. Cancer complexity was similar for the study cohorts before and after IPTW (Table 2). Year of index TKI initiation remained significantly different between the study cohorts ($P=0.002$) and therefore was included in the regression models.

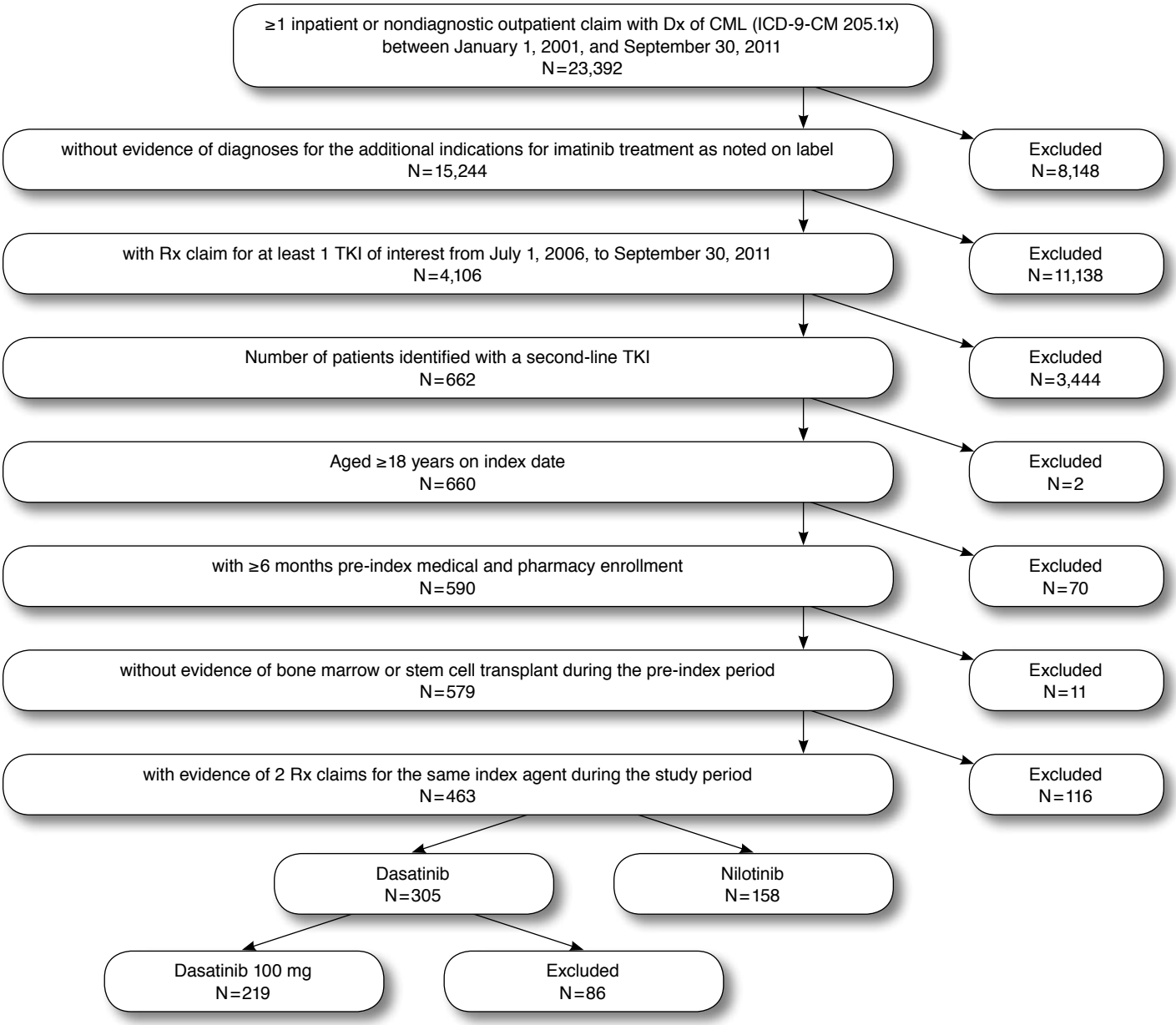
Length of follow-up was similar for the study cohorts before accounting for the patient weights (dasatinib 9.3 ± 3.5 months vs. nilotinib 9.1 ± 3.5 months, $P=0.621$). Overall, reasons for the end of follow-up (i.e., study end, end of enrollment, switch from index TKI, discontinuation, bone marrow/stem cell transplant, and 12 months post-index) were also similar ($P=0.057$).

Outcomes

The detailed results for all of the outcome measures after adjustment through propensity weighting can be found in Table 3.

Adherence. After propensity weighting, mean MPR was significantly higher among dasatinib than nilotinib patients (88.2% vs. 84.4%, $P=0.036$). In addition, high adherence (MPR ≥ 85%) occurred in a significantly greater percentage of dasatinib than nilotinib patients (72.7% vs. 63.3%, $P=0.006$). In the multivariate model (Figure 2), the likelihood of being highly

FIGURE 1 Sample Selection and Patient Attrition



CML = chronic myeloid leukemia; Dx = diagnosis; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; mg = milligram; Rx = pharmacy; TKI = tyrosine kinase inhibitors.

adherent among dasatinib patients was 1.7 times (95% CI = 1.2-2.4) greater than among nilotinib patients after accounting for the propensity weights and other covariates ($P = 0.0016$). The only other significant predictors of high adherence were aged 51-64 years (OR = 2.8; 95% CI = 1.4-5.6) and aged 65 years and older (OR = 2.5; 95% CI = 1.2-5.1) compared with patients aged 18-30 years.

Persistence. Mean PDC was not significantly different between dasatinib and nilotinib patients (0.79 vs. 0.77, $P = 0.328$) after propensity weighting. However, ELPT (based on an allowed gap of 1.5 times the days' supply between each prescription fill) showed that a significantly higher percentage of dasatinib patients remained persistent (had no treatment interruptions) throughout their follow-up periods (70.4% compared with

TABLE 1 Demographic Characteristics (IPTW)

Characterisitics	Dasatinib N = 219		Nilotinib N = 158		*P* Value
Age[a] (mean, SD)	54.2	21.1	54.4	21.3	0.887
Age cohort (n, %)					
18-30	16	7.1	8	4.9	0.038
31-40	29	13.2	20	12.6	
41-50	44	20.1	27	17.2	
51-64	75	34.2	71	45.1	
≥65	55	25.3	32	20.2	
Sex[a] (n, %)					
Male	118	53.8	87	55.2	0.695
Female	101	46.2	71	44.8	
Population density (n, %)					
Urban	191	87.2	125	79.4	0.016
Rural	26	11.8	30	19.1	
Unknown	2	1.0	2	1.5	
Geographic region[a] (n, %)					
Northeast	29	13.1	19	12.3	0.836
North Central	52	23.9	37	23.6	
South	82	37.6	56	35.3	
West	53	24.3	43	27.3	
Unknown	2	1.0	2	1.5	
Health plan type[a] (n, %)					
Fee-for-service	27	12.3	19	11.8	0.986
HMO	43	19.7	31	19.8	
PPO/EPO	123	56.2	91	57.5	
POS	11	5.1	6	3.9	
CDHP/HDHP	7	3.3	5	3.4	
Other/unknown	7	3.4	6	3.6	
Primary payer (n, %)					
Commercial	163	74.4	123	77.8	0.268
Medicare	56	25.6	35	22.2	

[a]*Represents measures used in the propensity model.*

CDHP = consumer driven health plan; EPO = exclusive provider organization; HDHP = high-deductible health plan; HMO = health maintenance organization; IPTW = inverse probability treatment weighting; POS = point of service; PPO = preferred provider organization; SD = standard deviation.

62.7% of nilotinib patients, $P = 0.026$). Furthermore, dasatinib patients were found to be more persistent than nilotinib patients using an allowed gap of 2 times the days' supply between each prescription fill for ELPT (83.7% vs. 77.6%, $P = 0.033$).

Discontinuation. Based on the 90-day gap definition of discontinuation, a significantly lower proportion of dasatinib patients discontinued therapy compared with nilotinib patients (4.4% vs. 8.6%, $P = 0.020$). Although time to discontinuation was not significantly different between the 2 cohorts, a Cox proportional hazards model adjusting for additional covariates showed dasatinib patients discontinuing treatment at half the rate per unit time of nilotinib patients (HR = 0.50; 95% CI = 0.27-0.93; $P = 0.029$). The results of both sensitivity analyses did not show significant differences in discontinuation outcomes between the 2 cohorts. First, using a 60-day gap discontinuation definition, rates of the 2 cohorts were similar (dasatinib 31.4% vs. nilotinib 35.1%, $P = 0.283$). Also, when the cohorts were expanded to include patients with only 1 prescription fill for their index TKIs and a 90-day gap for discontinuation, rates did not differ significantly (7.2% dasatinib vs. 9.0% nilotinib, $P = 0.762$).

Discussion

Current management guidelines state that if resistance to BCR-ABL inhibitors is encountered, then the possibility of nonadherence to treatment should be investigated.[1] Using recognized measures of adherence and persistence and accounting for imbalances in baseline patient characteristics, second-line dasatinib-treated patients had significantly higher adherence rates than nilotinib patients within the first year following second-line treatment initiation. In addition, dasatinib patients were 1.7 times more likely to be highly adherent and had half the chance of discontinuing treatment compared with nilotinib patients at any point in time.

Stem cell transplant is currently the only cure for CML. Since this is not often an available option, it is important for patients to remain adherent to TKIs, since lifelong medical treatment is necessary to prevent disease progression.[5] In studies of adherence to imatinib therapy, correlations between poor adherence, reduced failure-free survival, and increased health care costs have been identified.[6-10] Dasatinib and nilotinib were approved in 2006 and 2007, respectively, for the treatment of CML patients who developed resistance or intolerance to imatinib. There have been a few studies comparing adherence and persistence to these second-line therapies, but the results have not proved consistent in direction or magnitude.

Two studies utilizing retrospective claims data demonstrated adherence to second-line dasatinib was significantly higher than second-line nilotinib among patients with CML. Utilizing similar methods for measuring adherence among patients in the Invision Data Mart and PharMetrics administrative claims databases, Trivedi et al. (2012) reported levels of high adherence (MPR ≥ 85%) among dasatinib and nilotinib patients (75% vs. 61%) that are similar to those that were found in this analysis.[21] Persistence, however, while directionally similar, was much lower than reported here (47% dasatinib vs. 39% nilotinib). The authors did not perform multivariate analyses or account for potential cohort imbalances. Using Cox proportional hazard models, Yood et al. (2012) found that patients in the HealthCore database receiving second-line nilotinib were almost twice as likely to have poor adherence (MPR < 85%) than those receiving second-line dasatinib.[11] In addition, the study showed that adherence to oral CML treatment declined as the duration of treatment increased.

Two other studies have reported adherence and persistence results directionally different to the findings of this analysis and the aforementioned studies, with nilotinib patients having significantly greater adherence and persistence to treatment than dasatinib patients. Although our study did not find PDC to be

TABLE 2 Clinical Characteristics (IPTW)

Characteristics	Dasatinib (N = 219)		Nilotinib (N = 158)		*P* Value
Index year (n, %)					
2006	5	2.5	0	0.0	0.002
2007	15	6.8	5	3.5	
2008	40	18.3	26	16.7	
2009	51	23.4	31	19.6	
2010	67	30.5	62	39.3	
2011	40	18.5	33	20.8	
CML year of diagnosis[a] (n, %)					
2001	4	2.0	4	2.4	0.891
2002	6	2.8	5	2.9	
2003	2	1.1	0	0.0	
2004	6	2.7	4	2.5	
2005	12	5.4	8	5.2	
2006	20	9.3	14	9.1	
2007	27	12.4	18	11.3	
2008	57	26.0	42	26.6	
2009	42	19.1	31	19.3	
2010	33	15.1	24	15.5	
2011	9	4.0	8	5.3	
Months of first-line treatment[a] (mean, SD)					
Imatinib	18.9	18.6	20.1	26.0	0.464
Dasatinib	N/A	N/A	14.9	14.5	N/A
Nilotinib	10.9	8.0	N/A	N/A	N/A
Days between first-line and second-line treatment (mean, SD)	34.4	21.8	33.1	25.3	0.464
Comorbidities of interest (n, %)					
Depression	5	2.2	5	3.3	0.354
Anxiety	1	0.3	0	0.0	0.301
Overall mental health[a]	13	6.0	10	6.6	0.720
Osteoarthritis[a]	4	1.8	3	2.0	0.861
Asthma/COPD[a]	7	3.1	6	3.9	0.563
Diabetes[a]	17	7.6	13	8.0	0.863
Hypertension	19	8.8	17	10.7	0.387
Ischemic heart disease	12	5.7	4	2.5	0.029
Congestive heart failure	6	2.7	5	2.9	0.883
Stroke	1	0.5	3	1.8	0.113
Any CVD[a]	54	24.8	40	25.1	0.921
Low back pain[a]	10	4.6	7	4.7	0.947
GI disease[a]	19	8.5	13	8.5	0.996
Deyo Charlson Comorbidity Index (mean, SD)	2.5	1.5	2.3	1.6	0.156
Cancer complexity[a] (n, %)					
Usual	158	72.4	114	71.9	0.988
Moderate	40	18.2	29	18.6	
High	21	9.5	15	9.6	
Number of unique therapeutic drug classes[a] (mean, SD)	6.7	5.6	6.7	7.9	0.996
Duration of follow-up in months (mean, SD)	9.2	4.6	9.2	5.4	0.939
Reason for end of follow-up period (n, %)					
End of enrollment	53	24.3	30	19.2	0.055
End of study data period, December 31, 2011	24	11.2	21	13.6	
Switch from index treatment	23	10.4	11	7.0	
Discontinuation	10	4.4	14	8.6	
Bone marrow/stem cell transplant	4	2.0	3	1.7	
Reached end of 12 months post-index date	105	47.8	79	50.0	

[a]*Represents measures used in the propensity model.*

CML = chronic myeloid leukemia; COPD = chronic obstructive pulmonary disease; CVD = cardiovascular disease; GI = gastrointestinal; IPTW = inverse probability treatment weighting; N/A = not applicable; SD = standard deviation.

TABLE 3 Measures of Adherence (IPTW)

	Dasatinib N = 219		Nilotinib N = 158		*P* Value
Medication possession ratio					
Mean, SD	0.88	0.21	0.84	0.28	0.036
Low adherence: <85% (n, %)	60	27.3	58	36.7	0.006
High adherence: ≥85% (n, %)	159	72.7	100	63.3	
Measurement of persistence					
Proportion of days covered, mean, SD	0.79	0.26	0.77	0.32	0.328
Estimated level of persistence					
Subsequent script within 1.5x days' supply (n, %)					
Treatment interruption	65	29.6	59	37.3	0.026
Persistent	154	70.4	99	62.7	
Subsequent script within 2x days' supply (n, %)					
Treatment interruption	36	16.3	35	22.4	0.033
Persistent	183	83.7	123	77.6	
Discontinuation: ≥2 fills (n, %)					
Treatment gap of 60 days	69	31.4	55	35.1	0.282
Treatment gap of 90 days	10	4.4	14	8.6	0.021
Days to discontinuation, mean, SD	165.1	79.5	153.2	77.6	0.623

IPTW = inverse probability treatment weighting; SD = standard deviation

significantly different between dasatinib and nilotinib patients over 12 months following treatment initiation, Wu et al. (2010) reported that second-line dasatinib-treated patients were less persistent than those treated with nilotinib (PDC = 0.69 vs. 0.79, $P < 0.007$) over the first 6 months of treatment.[9] There were several methodological limitations in that study that were addressed in a follow-up by study by Guérin et al. (2012).[12]

Updates in the Guérin et al. study included extending the study period to 12 months, stratifying the dasatinib index dose (140 mg or ≤ 100 mg daily), and confirming second-line treatment with nilotinib and dasatinib by looking for prior use of imatinib. Outcome measures now included MPR, which was calculated in accordance with the ISPOR guidelines, and second-line dasatinib patients had lower adherence than nilotinib patients (MPR = 0.75 vs. 0.80, $P = 0.018$). PDC was again significantly higher for nilotinib (0.76 vs. 0.71, $P = 0.022$), although slightly more favorable for dasatinib than the original results. When comparing the results of the current study presented here to the Guérin et al. study, there was no difference in PDC across the products. The mean MPR was 4 points greater in the nilotinib cohort (0.84 vs. 0.80) and 13 points higher in the dasatinib cohort (0.88 vs. 0.75), although the reasons for these differences are unclear.

Our study found that the proportion of patients discontinuing second-line nilotinib treatment was twice that of second-line dasatinib. Use of multivariate modeling further supported this finding. Wu et al. reported the opposite finding that dasatinib patients had twice the discontinuation rate of nilotinib patients. In that study, dasatinib patients had twice the rate of cardiovascular disease at baseline (21.2% vs. 10.1%, $P = 0.031$); however, only the Charlson Comorbidity Index, which showed no significant differences between the groups, was included in the multivariate model. In addition, for Wu et al. and Guérin et al., only 30 days of enrollment post-index was required for study inclusion, approximately equal to 1 prescription fill, rather than the 2 consecutive fills required for inclusion here. However, while Wu et al. found higher rates of dasatinib discontinuation, dasatinib patients had significantly longer days of follow-up compared with nilotinib patients in both studies. There was an excess of 19.7 days in the 6-month follow-up and 26.9 days in the 12-month follow-up. Interestingly, the differences in PDC, when converted to days of coverage difference, are 17 days and 22 days fewer for dasatinib patients, respectively, for the 2 studies.

When sensitivity analyses were run in our study for the discontinuation outcomes to include patients with only a single prescription fill for dasatinib or nilotinib, differences in rates of discontinuation were no longer statistically significant (7.2% vs. 9.0%, $P = 0.762$). In addition, while mean time to discontinuation remained similar, dasatinib patients were found to discontinue treatment on average 26 days earlier (median 36 days) than nilotinib patients. Considering the findings of our study and those of Wu et al. and Guérin et al., it may be that once patients initiating second-line treatment with dasatinib remain on treatment for at least 60 days, they experience lower rates of discontinuation, higher rates of persistence, and increased likelihood of adherence compared with patients similarly treated with nilotinib.

Both the Wu and Guérin studies utilized 2 databases in order to increase sample size. MarketScan data were merged with the Ingenix/IHCIS Impact National Managed Care Database (Wu et al.[9]) and PharMetrics (Guérin et al.[12]). MarketScan and these other databases are not known to be mutually exclusive; therefore, it is possible that the same patient may be found in each source. The potential impact of certain patients being included multiple times in the analysis is not addressed in the limitations of either study. The MarketScan databases include claims data provided by large self-insured employers representing enrollees in hundreds of unique health plans, whereas the Ingenix/Impact include claims data primarily from a more limited number of health plans. Therefore, if formulary designs and restrictions impact the use of one TKI compared with another, including duplicate patients may bias the results in a single direction.

For the study present study, IPTW was utilized to minimize potential selection biases. A few differences in the populations remained—index year and population density. These were included in the model of high adherence, but neither was associated with the outcome. While there was no difference between the populations in age as a continuous measure, age group was significantly different. As age has been shown to be associated with adherence to therapy for chronic disease, the decision was made to include age group in the model predicting adherence.[5] Patients aged 51-64 years and 65 years and older were more likely to be highly adherent (MPR ≥ 85%) than patients aged 18-30 years at initiation of second-line treatment.

FIGURE 2 Adjusted Probability of High Adherence (MPR ≥ 85%)[a]

Note: Reference groups: TKI = nilotinib, cancer complexity = usual, Index Year ≤ 2008, Urbanicity = Urban/Unknown, Age Group = 18-30.

[a]*Where the complete line lies to the right of 1.0, the odds of the outcome are significantly greater than the comparison group; if to the left of 1.0, the odds are significantly lower than the comparison group; and where the line crosses 1.0, the odds ratio is not significantly different.*

MPR = medication possession ratio.

Treatment-related barriers to adherence include dose frequency or complexity, the latter including polypharmacy, which has been shown to be negatively correlated with adherence to imatinib.[20] It may also lead to increased toxicity through drug-drug interactions.[5] Patient medication burden was also included in the model and was negatively associated with high adherence but did not reach statistical significance.

Limitations

Several limitations to these analyses merit consideration. First, while use of propensity weights in the analyses resulted in more balanced dasatinib and nilotinib populations, some patient characteristics remained imbalanced. These were not, however, shown to be associated with the outcome of high adherence. Weights were also used as opposed to propensity score matching in order to retain the sample size and, therefore, power to detect significant differences. It is not known if the study conclusions would have been different if propensity score matching had been implemented. Second, certain limitations are inherent to all claims databases. Because they depend on reimbursement coding practices of physician offices, outpatient pharmacies, and hospitals, potential miscoding of medical claims and missing data, which cannot be verified through medical chart review, are possible. However, there is no reason to expect systematic differences in patients treated with nilotinib or dasatinib. Administrative data also are collected for financial and administrative rather than research purposes. As such, they do not provide insights into clinical variables of interest such as phase of CML, response to oral TKI treatment, or reasons for nonadherence, which could be patient-, treatment-, or physician-driven. Finally, the study population includes patients with commercial and Medicare supplemental insurance; thus, the results might not be generalizable to people with other types of insurance or with no insurance. Although numerous studies have used claims databases to meet objectives similar to those of this study, the most accurate assessment would likely include a review of medical chart records or prospective studies.

Conclusions

Utilizing recognized measures and methods to evaluate patient adherence and persistence using administrative claims data, we found that patients receiving second-line dasatinib treatment for CML had higher adherence and lower discontinuation rates compared with comparable patients receiving second-line nilotinib. As discussed in this article, similar and conflicting findings have been identified between this study and others in the literature with respect to adherence and persistence. However, patient selection and methodological differences across the studies make direct comparison of results difficult. Additional studies are warranted using similar measures of adherence and persistence in larger patient samples to confirm or refute the findings presented here.

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DISCLOSURES

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APPENDIX Exclusion Criteria, Independent Variables, and Covariates

Variables	Use in Propensity Model	Time Period for Measurement	Methods and Notes
Second-line TKI	x	July, 1, 2006-September 30, 2011	Dasatinib: NDC 00003052411, 00003052711, 00003052811, 00003085222, 00003085522, 00003085722, 54868575900
			Nilotinib: NDC 00078052651, 00078052687, 00078059251, 00078059287
Index year		2006-2011	Year of first second-line TKI prescription fill
Bone marrow or stem cell transplant		6-month pre-index period and follow-up period	CPT-4 codes: 38240, 38241, 38242 ICD-9-CM diagnosis codes: 996.85, V42.81 ICD-9-CM procedure codes: 41.00-41.09
Relapsed or refractory Philadelphia chromosome–positive acute lymphoblastic leukemia (Ph+ALL)		2001-2011	ICD-9-CM: 204.00, 204.01, 204.02
Myelodysplastic/myeloproliferative diseases (MDS/MPD) associated with PDGFR (platelet-derived growth factor receptor) gene rearrangements			ICD-9-CM: 238.7, 238.72-238.75, 238.79
Aggressive systemic mastocytosis (ASM) without the D816V c-KIT mutation or c-KIT mutational status unknown		2001-2011	ICD-9-CM: 202.60-202.68
Hypereosinophilic syndrome (HES) and/or chronic eosinophilic leukemia (CEL) who have FIP1L1-PDGFRα fusion kinase (mutational analysis or FISH demonstration of CHIC2 allele deletion) and for patients with HES and/or CEL who are FIP1L1-PDGFRα fusion kinase negative or unknown		2001-2011	ICD-9-CM: 288.3
Adult patients with unresectable, recurrent, and/or metastatic dermatofibrosarcoma protuberans (DFSP)		2001-2011	ICD-9-CM: 235.1, 235.5, 236.3, 236.6, 238.2
KIT (CD117)-positive unresectable and/or metastatic malignant gastrointestinal stromal tumors (GIST)		2001-2011	ICD-9-CM: 171.5
CML year of diagnosis	x	2001-2011	Year of service date for first identified nondiagnostic medical claim with ICD-9-CM: 205.1x
Length of first-line TKI treatment	x	2001-2011	Total days' supply for all prescription claims for first-line imatinib (NDC 00078037366, 00078040105, 00078040134, 00078040215, 00078043815, 54868528900, 54868528901, 54868528902, 54868528903, 54868528904, 54868542700, 54868542701, 54868542702, 54868542703, 54569584600, 68258902801), dasatinib, or nilotinib
Demographic characteristics	x	Index date	Age as a continuous measure identified on index TKI claim
			Age group: 18-30, 31-40, 41-50, 51-64, ≥65
	x		Gender: male or female
	x		Region: U.S. census region based on patient state of residence on index TKI claim (North, South, North Central, West)
	x		Type of health plan: indemnity, PPO/EPO, POS, HMO, HDHP/CDHP as noted on index TKI claim

APPENDIX Exclusion Criteria, Independent Variables, and Covariates *(continued)*

Variables	Use in Propensity Model	Time Period for Measurement	Methods and Notes
Baseline comorbidities	x	6-month pre-index period	Binary indicators for: Depression: ICD-9-CM 296.2x, 296.3x, 300.4x, 311.xx recorded on any medical claim
	x		Anxiety: ICD-9-CM 300.0x, 300.2x, 300.3x, 308.3x, 309.21, 309.81, 293.84 recorded on any medical claim
	x		Overall mental health: ICD-9-CM 290.xx-319.xx, V61.xx, V62.xx, V71.0, V65.42
	x		Osteoarthritis: ICD-9-CM 715.xx
	x		Asthma/COPD: ICD-9-CM 493.xx, 496.xx, 491.21, 491.22
	x		Diabetes: ICD-9-CM 250.xx
	x		Hypertension: ICD-9-CM 401.xx-405.xx, 437.2x
	x		Ischemic heart disease: ICD-9-CM 410.xx-414.xx
	x		Congestive heart failure: ICD-9-CM 398.91, 428.xx
	x		Stroke: ICD-9-CM 433.x1-434.x1, 435.xx, 436.xx, 438.xx, 437.1x, 437.9x
	x		Any cardiovascular disease: ICD-9-CM 390.xx-459.xx, 782.3x, 796.2x, 786.50
	x		Low back pain: ICD-9-CM 720.0x, 720.2x, 721.3x, 722.0x, 722.32, 722.52, 722.73, 722.83, 722.93, 724.02, 724.2x, 724.3x, 724.6x, 724.7x
	x		Gastrointestinal disease: ICD-9-CM 530.xx-537.xx, 578.0x, 789.0x
Deyo-Charlson Comorbidity Index		6-month pre-index period	Range 0-32
Cancer complexity (Darkow et al. 2007[8])	x	6-month pre-index period	Usual Moderate High
Total number of prescription therapeutic classes	x	6-month pre-index period	Sum of unique RED BOOK therapeutic classes assigned to prescription claims[a]
Duration of follow-up for each treatment cohort		Post-index period	Months

[a]*RED BOOK's therapeutic classes facilitate retrieval of products with similar therapeutic uses; searches can be conducted by NDC for broad categories, such as cardiovascular agents, or for more specific topics such as angiotensin-converting enzyme inhibitors and beta blockers. See: http://www.redbook.com/redbook/.*

CDHP = consumer driven health plan; CML = chronic myeloid leukemia; COPD = chronic obstructive pulmonary disease; CPT-4 = Current Procedural Terminology, 4th edition; EPO = exclusive provider organization; HDHP = high-deductible health plan; HMO = health maintenance organization; ICD-9-CM = International Classification of Diseases, Ninth Revision, Clinical Modification; NDC = National Drug Code; POS = point of service; PPO = preferred provider organization; TKI = tyrosine kinase inhibitors.