Acta Haematologica

Original Paper

Acta Haematol
DOI: 10.1159/000530512

Received: October 14, 2022
Accepted: March 27, 2023
Published online: April 10, 2023

An Analysis of Dasatinib Treatment Patterns in Patients with Chronic Myeloid Leukemia after Experiencing Pleural Effusion during Dasatinib Therapy

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Keywords
Chronic myeloid leukemia · Hematological malignancies · Malignant hematology

Abstract
Introduction: Treatment with dasatinib for chronic myeloid leukemia (CML) has been associated with development of pleural effusion; however, data regarding its optimal management are limited. We examined treatment patterns and healthcare resource utilization (HCRU) and costs among patients with CML treated with dasatinib who experienced a subsequent pleural effusion. ***Methods:*** Adults with CML and ≥1 pharmacy claim for dasatinib in 2015–2018 who experienced pleural effusion after dasatinib were identified using data from claims databases. ***Results:*** Overall, 123 patients were eligible. After 1 year, of the 38.2% of patients with a dose modification, 72.3% did not switch treatment; among these patients, 70.6% continued treatment. Among patients with a stable dose after pleural effusion (61.8%), 57.9% later switched to another TKI. The mean (SD) duration of dasatinib treatment after pleural effusion was 262.0 (124.0) days for patients with a dose modification versus 149.1 (155.2) days for those with a stable dose ($p < 0.001$). HCRU and costs were similar between groups. ***Conclusion:*** Dasatinib dose modification after pleural effusion was not always required; however, patients with dose modifications continued therapy for a longer duration with a lower rate of switching to another TKI versus patients who remained on a stable dose.

Introduction

In 2022, approximately 8,860 people are expected to be diagnosed with chronic myeloid leukemia (CML) in the USA, representing about 15% of all new leukemia cases [1, 2]. Treatment decisions for patients with CML are dependent on many factors including disease phase, patient risk factors (e.g., age, cytogenetic abnormalities, comorbidities), drug tolerability, and adherence associated with convenience in dosing and administration [3–6]. Since the introduction of imatinib, a tyrosine kinase inhibitor (TKI), in 2001, and subsequent second-generation TKIs such as dasatinib (2006), nilotinib (2007), and bosutinib

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(2012), the survival outcomes for patients with CML have greatly improved [6–10].

Dasatinib is a highly potent selective inhibitor of the unmutated *BCR*::*ABL* kinase, and, based on the deep and durable responses reported in the phase 3 DASISION trial [11], an effective long-term treatment option for most patients with newly diagnosed CML. However, dasatinib treatment is associated with the development of pleural effusion, an adverse event characterized by the build-up of excess fluid in the pleural space outside of the lungs. In the DASISION trial, after a minimum follow-up of 60 months, 28% of dasatinib-treated patients experienced pleural effusion compared with 0.8% of imatinib-treated patients [11]. Currently, there is limited understanding of how to manage pleural effusion optimally while also achieving maximum clinical benefit in dasatinib-treated patients. Common strategies include dose reductions, dose interruptions, or switching to another TKI. Recently, results from the SIMPLICITY trial, a 3-year observational real-world study assessing treatment patterns in European patients with CML in the chronic phase in routine clinical practice, showed that patients who remained on first-line TKI treatment had better clinical outcomes than patients who switched treatment [12].

The aim of this study was to understand the optimal strategy for dasatinib treatment after pleural effusion in patients with CML. This was achieved through examining dasatinib treatment patterns, including duration of dasatinib use after pleural effusion, and healthcare resource utilization (HCRU) and costs among patients with CML treated with dasatinib who experienced a subsequent pleural effusion.

Methods

Data Source and Study Design

This was a retrospective study conducted using administrative claims data from the IBM MarketScan® Commercial and Medicare Supplemental databases during the study period between January 1, 2014, and September 30, 2019. The IBM MarketScan® Commercial and Medicare Supplemental Databases include medical and pharmacy claims for more than 39.7 million unique individuals and their dependents who are covered through employer-sponsored health insurance plans (fee-for-service and capitated) across the USA for the most recent year of complete data [13]. The Medicare Supplemental database contains the healthcare experience of individuals with Medicare Supplemental insurance paid for by employers (both Medicare-covered and employer-paid portions are included in this database) [13]. Both databases are Health Insurance Portability and Accountability (HIPAA)-compliant administrative claims databases and the databases contain de-identified adjudicated pharmacy claims.

Study Population

Patients were included if they had ≥1 inpatient or ≥2 outpatient medical claims with a diagnosis code of CML (International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] codes: 205.1x, 205.8x; 10th Revision [ICD-10-CM] codes: C92.1x, C92.Zx), had ≥1 pharmacy claim for dasatinib during the study period, and experienced a pleural effusion (ICD-9-CM: 511.1, 511.89; ICD-10-CM: J90) after dasatinib treatment during the identification (ID) period (January 1, 2015, to September 30, 2018).

All patients had ≥1 filled prescription for dasatinib before the index date (date of the first pleural effusion during the ID period), with dasatinib available on the index date, and did not have a code for pleural effusion during the baseline period (1-year pre-index). Patients were required to be ≥ 18 years of age as of the index date and continuously enrolled during baseline and follow-up (1-year post-index) periods (Fig. 1).

The treatment cohorts were broadly defined based on whether patients experienced a dasatinib dose modification or remained on a stable dose of dasatinib. Dose modification was defined as the presence of either a dose interruption (defined as a gap of 15–59 days in dasatinib use) or a dose reduction (defined as a reduction in the average daily dose between the last fill of dasatinib before the index date and the first dasatinib dose modification after the index date). The occurrence of a dose modification was determined from the index date until a treatment switch to another TKI, or the end of the follow-up period if no switch occurred. In the case of multiple dose modifications, the first dose modification was used. Patients who remained on a stable dose of dasatinib were those without any dose modification, including patients without a new dasatinib fill, during the follow-up period. Discontinuation of therapy was defined as a gap in use of ≥60 days without dasatinib after exhausting the current supply.

Study Measures

Treatment Patterns, Healthcare Utilization, and Cost

The following treatment pattern outcomes were evaluated among the dose modification and stable dose cohorts during the follow-up period: proportion of patients switching from dasatinib to a different TKI and time to a TKI switch; proportion of patients continuing (and discontinuing) dasatinib treatment without a switch to another TKI; and duration of dasatinib therapy (defined as the number of days from the first pleural effusion to the end of dasatinib use). Among patients with a dose modification, times from pleural effusion until modification and from modification to end of treatment were examined.

HCRU (i.e., hospitalization, length of hospital stay, emergency department [ED] visits, and physician office visits) and cost (i.e., total, inpatient, outpatient, and pharmacy costs) were also evaluated for the study cohorts during the follow-up period. To assess the clinical management of pleural effusions, frequency of use of corticosteroids, diuretics, oxygen therapy, and/or pleural procedures (e.g., thoracentesis, pleurodesis, fluid drainage) was evaluated during the follow-up period (see online suppl. Table S1; for all online suppl. material, see https://doi.org/10.1159/000530512 for procedure codes).

Baseline Characteristics

Patient demographics, health insurance type, primary physician specialty, and clinical characteristics, including the Charlson

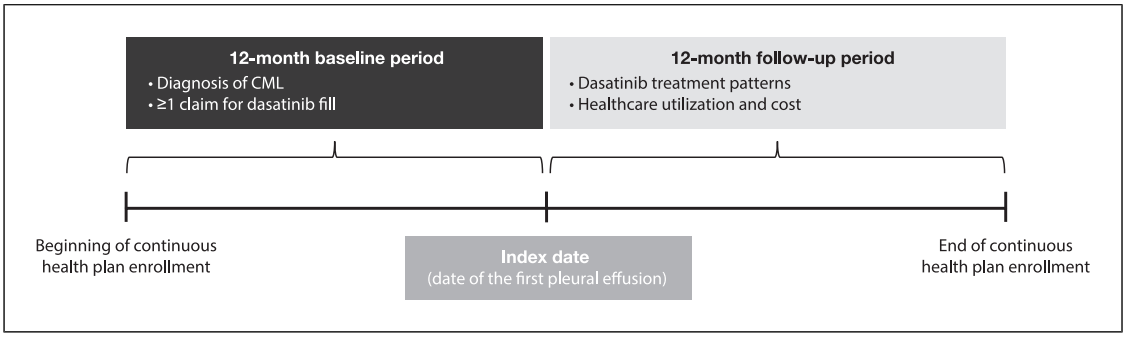

Fig. 1. Study design. CML, chronic myeloid leukemia.

Comorbidity Index (CCI) score, use of another TKI prior to dasatinib use, and average daily dose of index dasatinib, were assessed during the baseline period.

Statistical Analysis

Descriptive statistics were generated for all measures and reported for all patients and each study cohort. Means and standard deviations (SDs) were reported for continuous variables, and relative frequencies and percentages for categorical data. Statistical testing was conducted using χ^2 (exact χ^2 if a cell count was <5 or *t*-tests). Time to switch and discontinuation in patients with and without a dose modification was compared using Kaplan-Meier estimation and plots. All data transformations and statistical analyses were performed using SAS© version 9.4 (SAS Institute Inc., Cary, NC, USA). A sensitivity analysis was conducted to examine whether pleural effusion was under-coded. This was done by assessing the number of patients identified with possible drug-related pleural effusion through evidence of shortness of breath along with a radiology procedure or a specific diagnosis code for pleural effusion.

Results

Baseline Characteristics

During the ID period, there were 542 patients who had at least one dasatinib claim with pleural effusion. After using a sensitivity analysis with specific definitions for pleural effusion claims, 347 patients were identified (online suppl. Table S2). A total of 123 patients met all study criteria and were included in the analysis (online suppl. Table S2). Of these patients, 47 (38.2%) had a dose modification of dasatinib and 76 (61.8%) maintained a stable dose of dasatinib after pleural effusion (Fig. 2). Patient demographics and clinical characteristics in all patients and by study cohort are shown in Table 1. Overall, the mean (SD) age was 62.2 (10.9) years, 23.6% were female, the mean (SD) CCI was 3.8 (2.1), and the mean (SD) number of chronic conditions was 6.0 (2.4). Most patients were covered by commercial/private insurance (64.2%), and more patients were treated by a physician specializing in hematology/oncology (41.5%) than any other physician specialties (primary care physician: 18.7%; internist: 17.1%; other: 22.7%). The mean (SD) prescribed daily dose of dasatinib at index was 94.6 (23.3) mg. Seventeen patients (13.8%) had used another TKI prior to the first observed dasatinib fill, with imatinib being the most frequently used prior to TKI (n = 12; 9.8% patients). Mean (SD) time to the first pleural effusion from first dasatinib fill was 252.3 (125.0) days. None of the differences between cohorts were statistically significant due to small sample sizes.

To assess whether pleural effusion was under-coded, a sensitivity analysis was performed and identified 542 patients with evidence of shortness of breath and a radiology procedure or a specific code for pleural effusion. While neither methodology for identifying patients with CML and drug-related pleural effusion has been validated, the study's chosen approach was more conservative and likely captured patients with true, if more severe, drug-related pleural effusion for the full analysis.

Dasatinib Treatment Patterns during the 1-Year Follow-Up Period

At the 1-year follow-up, of the 47 patients who had a dose modification, most (n = 34, 72.3%) did not switch treatment, and of these, 70.6% (n = 24) continued dasatinib treatment. Of the 76 patients who remained on a stable dose after development of a pleural effusion, 57.9% (n = 44) switched to another TKI; of the remaining 32 patients who did not switch, 75% (n = 24) continued dasatinib treatment (Fig. 2). Patients with a dose modification after pleural effusion had a significantly longer duration of dasatinib treatment (number of days from the first pleural effusion to end of dasatinib treatment) compared with

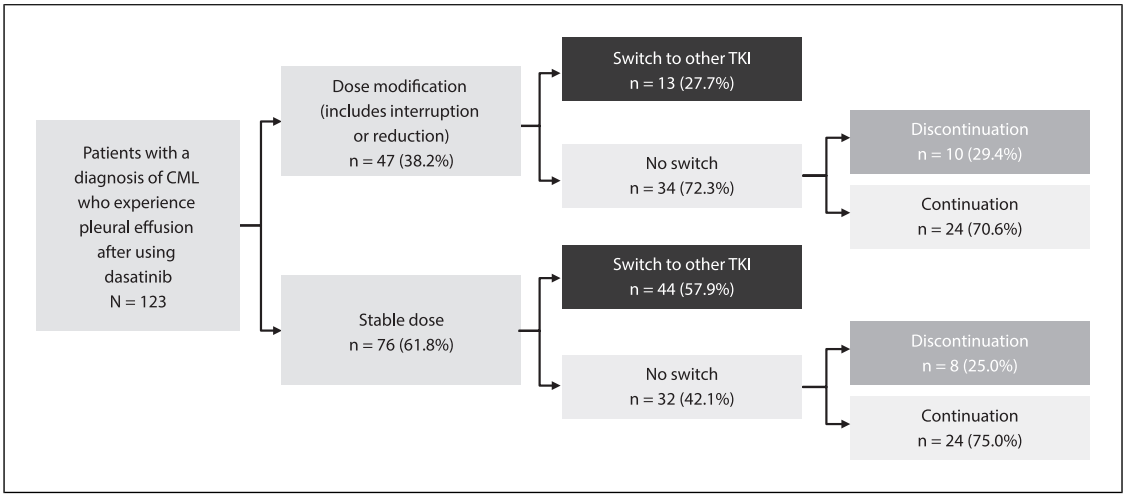

Fig. 2. Dasatinib treatment patterns after pleural effusion: 1-year follow-up. Dose interruption: defined as a gap in use of 15–59 days. Reduction: defined as reduction in average daily dose between last fill before index and first dose modification after index. Discontinuation: defined as a gap in use of dasatinib of at least 60 days after exhausting current supply and among patients without a switch to another TKI; patients whose dasatinib use had a <60-day gap were considered to have continued use. Stable dose: defined as no modification to dasatinib dosing. CML, chronic myeloid leukemia; TKI, tyrosine kinase inhibitor.

Table 1. Patient demographics and clinical characteristics

	Dose modification (*n* = 47)	Stable dose (*n* = 76)	All (*N* = 123)
Age, mean (SD), years	62.1 (10.3)	62.3 (11.3)	62.2 (10.9)
Female, *n* (%)	11 (23.4)	18 (23.7)	29 (23.6)
Insurance type, *n* (%)			
Commercial/private	28 (59.6)	51 (67.1)	79 (64.2)
Medicare	19 (40.4)	25 (32.9)	44 (35.8)
Primary physician specialty[b], *n* (%)			
Hematologist/oncologist	21 (44.7)	30 (39.5)	51 (41.5)
Primary care physician[c]	10 (21.3)	13 (17.1)	23 (18.7)
Internist	6 (12.8)	15 (19.7)	21 (17.1)
Other[d]	10 (21.3)	18 (23.7)	28 (22.7)
CCI, mean (SD)	3.5 (1.8)	4.1 (2.3)	3.8 (2.1)
Number of chronic conditions, mean (SD)	5.7 (2.5)	6.2 (2.4)	6.0 (2.4)
Prescribed daily dose of index dasatinib fill, mean (SD), mg	95.1 (15.9)	94.2 (27.0)	94.6 (23.3)
Non-dasatinib TKI use prior to the first observed dasatinib fill at baseline[e], *n* (%)	7 (14.9)	10 (13.2)	17 (13.8)
Time from the first observed dasatinib fill in the baseline period to the index date[f], mean (SD), days	256.9 (128.2)	249.4 (123.8)	252.3 (125.0)

CCI, Charlson Comorbidity Index; SD, standard deviation; TKI, tyrosine kinase inhibitor. [a]Differences between cohorts were not statistically significant ($p > 0.05$ for all variables). [b]Physician specialty with the largest number of office visits with evaluation and management services during baseline period. [c]Includes physician assistants and nurse practitioners. [d]Includes individual specialties with <2% (other) and unknown specialties (4 with no evaluation and management claims and 6 with unspecified specialty). [e]Patients could use more than one TKI in the baseline period. [f]The first observed fill for dasatinib may not represent the initiation of such treatment.

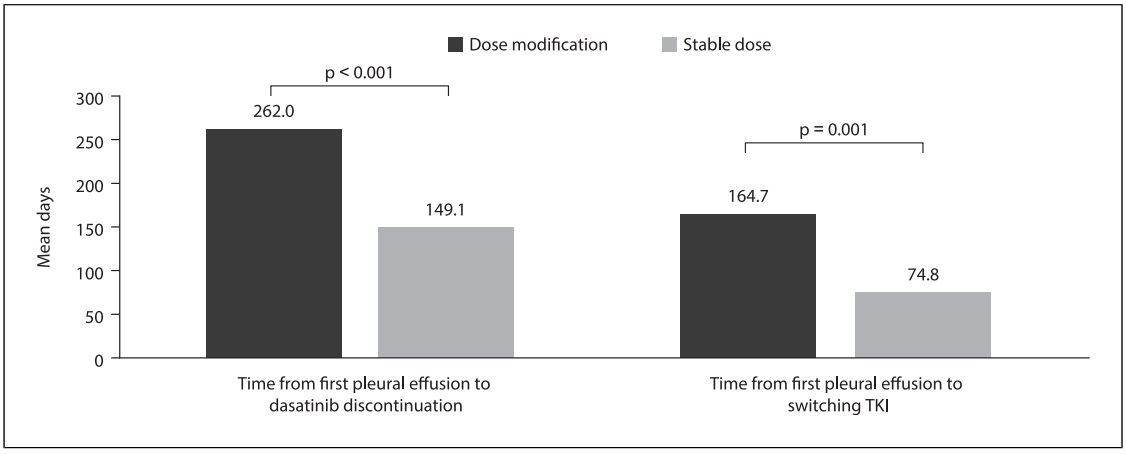

Fig. 3. Time to treatment event in patients with dose modification versus stable dose. TKI, tyrosine kinase inhibitor.

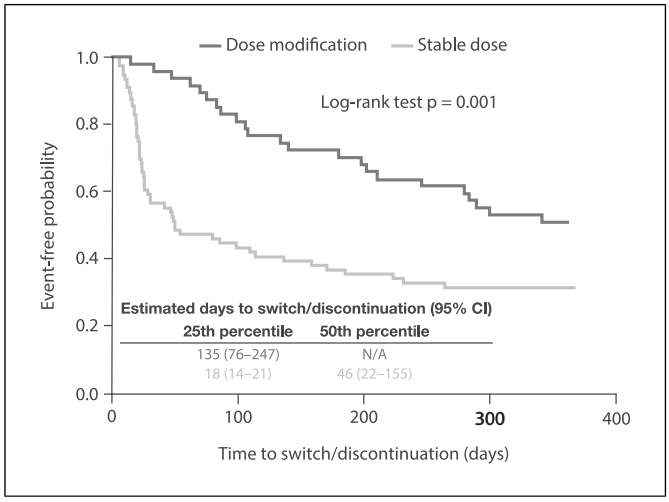

Fig. 4. Kaplan-Meier estimate of the duration of dasatinib treatment in patients with dose modification versus stable dose. CI, confidence interval; N/A, not available.

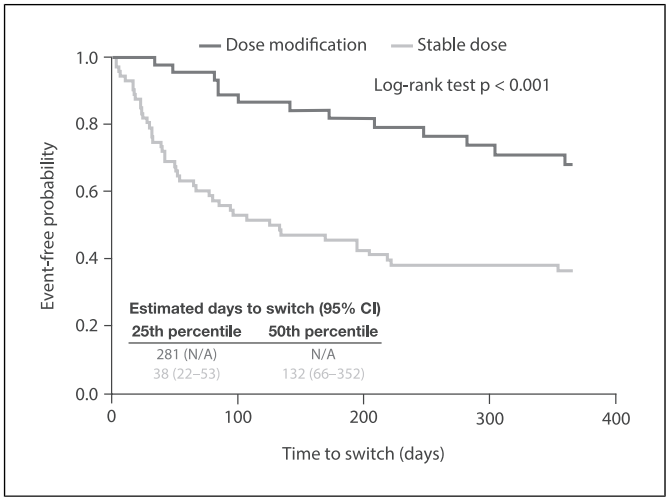

Fig. 5. Kaplan-Meier estimate of time to switch to another TKI in patients with dose modification versus stable dose. CI, confidence interval; N/A, not available; TKI, tyrosine kinase inhibitor.

patients who maintained a stable dose (mean [SD], 262.0 [124.0] vs. 149.1 [155.2] days; $p < 0.001$) (Fig. 3, 4).

Among patients who had a dose modification, the mean (SD) number of days from pleural effusion to dose modification was 73.7 (77.1) days and from dose modification to end of treatment was 188.3 (128.7) days. Among the patients who ended up switching treatment from dasatinib, those who had a dose modification were on dasatinib for a significantly longer time prior to switching compared with patients who remained on a stable dose (mean [SD], 164.7 [105.8] vs. 74.8 [76.0] days; $p = 0.001$) (Fig. 3, 5).

HCRU and Costs during the 1-Year Follow-Up Period

Overall, 48.0% of patients ($n = 59$) were hospitalized and 37.4% ($n = 46$) had an ED visit (Table 2). Patients spent a mean (SD) of 11.3 (14.3) days in hospital. The mean (SD) number of visits to the physician's office was 24.3 (16.7). Total mean (SD) costs were $196,797 ($143,848), with pharmacy costs being the major cost driver (mean [SD], $115,923 [$560,43]). There were no statistically significant differences in HCRU and costs between patients who had a dose modification and those with a stable dose (Table 2). Most patients who experienced pleural effusion

Table 2. Healthcare utilization and costs during the 1-year follow-up period[a]

	Dose modification (n = 47)	Stable dose (n = 76)	All (N = 123)
Healthcare visits			
Any hospitalization, n (%)	21 (44.7)	38 (50.0)	59 (48.0)
Total number of stays, mean (SD) [median], days	10.2 (12.8) [4]	11.8 (15.2) [6]	11.3 (14.3) [6]
Any ED visit, n (%)	20 (42.6)	26 (34.2)	46 (37.4)
Number of physician office visits, mean (SD) [median]	25.5 (16.5) [20]	23.6 (16.8) [19]	24.3 (16.7) [20]
Healthcare costs, mean (SD) [median]			
Total costs	$192,125 (143,419) [159,597]	$199,686 (144,988) [172,834]	$196,797 (143,848) [163,292]
Hospitalization costs	$39,885 (93,795) [0]	$41,315 (84,516) [4,096]	$40,769 (87,799) [0]
Outpatient care costs	$38,258 (56,468) [15,367]	$41,248 (60,315) [16,335]	$40,105 (58,658) [15,830]
Pharmacy costs	$113,982 (47,717) [124,969]	$117,123 (60,899) [113,546]	$115,923 (56,043) [114,607]
TKI costs	$106,143 (39,413) [117,407]	$107,146 (58,156) [110,967]	$106,763 (51,625) [112,167]
Pleural effusion treatment, n (%)			
Selected treatment for pleural effusion	42 (89.4)	62 (81.6)	104 (84.6)
Corticosteroids	28 (59.6)	34 (44.7)	62 (50.4)
Diuretics	23 (48.9)	41 (53.9)	64 (52.0)
Oxygen therapy	3 (6.4)	7 (9.2)	10 (8.1)
Pleural procedures (e.g., thoracentesis, pleurodesis, fluid drainage)	19 (40.4)	21 (27.6)	40 (32.5)

ED, emergency department; SD, standard deviation; TKI, tyrosine kinase inhibitor. [a]Differences between cohorts were not statistically significant ($p > 0.05$ for all variables).

received treatment (n = 104, 84.6%), including diuretics (n = 64, 52.0%) and corticosteroids (n = 62, 50.4%) (Table 2).

Discussion

The introduction of TKIs has had a profound impact on the treatment of CML, with patients now having the possibility of a near-normal life expectancy. The second-generation TKI dasatinib has been shown to be effective for long-term treatment of CML, both as first-line and as a subsequent-line treatment [11, 14]. However, treatment-related pleural effusion is more common with dasatinib than with other TKIs and can occur at any time during therapy. Most cases are mild to moderate, with only 2.7% of patients (n = 7/259) in the DASISION trial and 7.3% of patients (n = 28/662) in the CA180-34 dose optimization trial experiencing grade 3/4 pleural effusion [11, 15]. Pleural effusions can be well managed through treatment interruption, dose reduction, drug discontinuation, and other pharmacological management (steroids, diuretics, oxygen therapy, etc.) [16].

In this study, real-world data from a large insurance database of patients insured commercially or through Medicare in the USA were used to assess the management of pleural effusion experienced by patients with CML during dasatinib therapy. Dasatinib dose modification was associated with a longer duration of dasatinib treatment after pleural effusion and less frequent switching to another TKI, compared with maintaining a stable dose, indicating that dose modification can be an effective management strategy for patients with CML.

Treatment modification that allows patients to continue dasatinib therapy for a longer duration before switching (if necessary) is a plausible management option for patients who experience pleural effusion. This was shown in SIMPLICITY, an observational study of patients with CML in the chronic phase treated with first-line TKIs in routine clinical practice [12]. SIMPLICITY evaluated TKI treatment changes and how switching affects response outcomes. At the 3-year follow-up with the European cohort (n = 370), results showed that patients remaining on first-line TKI therapy were more likely to achieve better cytogenetic and molecular responses than those who switched therapy [12].

The healthcare costs associated with managing pleural effusions can vary greatly and are dependent on the severity of the pleural effusion. A previous claims-based real-world study found that pleural effusions did

not lead to higher overall healthcare costs than other adverse events associated with TKI treatment, such as femoral arterial stenosis, peripheral arterial occlusive disease, intermittent claudication, coronary artery stenosis, and pericardial effusion [17]. Although the study presented here did not evaluate healthcare costs specific to pleural effusion, the costs between the cohorts of patients who had a dose modification versus those who remained on a stable dose were not significantly different.

There are several limitations to this study. Pleural effusions captured through administrative claims may represent only the more severe cases (e.g., cases involving an ED visit or hospital stay), which may have resulted in an underreporting of pleural effusions following dasatinib treatment. Results from our sensitivity analysis supported this hypothesis: when patients with CML with evidence of shortness of breath along with a radiology procedure (two factors that could signal pleural effusion) were also included, a larger sample size of patients was identified. As neither approach has been validated, the more cautious approach was used in this study and likely captured patients who experienced true, if potentially more severe, drug-related pleural effusion. Also, correlative analysis was not performed in this study, hindering the ability of the study to assess the association of presence/absence of pleural effusion and dasatinib dose modification with treatment response. Additionally, the small sample size limited the ability to conduct multivariate analyses to adjust for factors that may explain the differences in treatment patterns between the two cohorts. Despite this limitation, descriptive results were reported to understand better the actual treatment patterns surrounding the infrequent event of a pleural effusion. Finally, administrative claims data did not capture the more comprehensive clinical data (e.g., laboratory results) that might potentially provide additional details on patient characteristics.

Conclusions

Patients who had a dose modification of dasatinib after development of pleural effusion were able to continue dasatinib treatment for a longer duration and had a lower rate of switching to another TKI (but with similar HCRU and costs) compared with patients who maintained a stable dose. However, approximately one-third of patients who maintained a stable dose after pleural effusion did not switch treatment. The results of this study demonstrate that not all patients require a dose modification to continue dasatinib treatment after pleural effusion, although in some patients, dose modification of dasatinib may provide continued treatment with the potential to sustain outcomes.

Acknowledgments

Writing and editorial assistance were provided by Flint Stevenson-Jones, PhD., of Caudex, funded by Bristol Myers Squibb.

Statement of Ethics

Ethical approval and consent were not required as this study was based on publicly available data. Patient consent was not required as this study was based on publicly available data.

Conflict of Interest Statement

A.M.: employee of Bristol Myers Squibb. J.B.: stock owner and former employee of Bristol Myers Squibb. S.R.R., E.C., and M.H.T.: employees of PHAR, LLC, which was paid by the following companies to conduct research: Bristol Myers Squibb, Celgene, GRAIL, Kite, Novartis. T.W.L.: grants or contracts to institution from AstraZeneca, Bristol Myers Squibb, CareVive, Jazz Pharmaceuticals, Seattle Genetics; royalties from UpToDate; consulting fees from AbbVie, Agilix, Agios/Servier, BeiGene, Bristol Myers Squibb/Celgene, BlueNote, Flatiron Health, Genentech, GlaxoSmithKline, Novartis, Pfizer; honoraria from AbbVie, Agios/Servier, Bristol Myers Squibb/Celgene; travel support from AbbVie, Agios/Servier, Bristol Myers Squibb/Celgene. Dr. LeBlanc is supported by a Scholar in Clinical Research from the Leukemia and Lymphoma Society.

Funding Sources

The study was supported by Bristol Myers Squibb.

Author Contributions

Ali McBride: interpreted the data, contributed to the development of the manuscript, approved the final version for publication, and had final responsibility for the decision to submit for publication. John Brokars, Eunice Chang, Marian H. Tarbox, Thomas W. LeBlanc, and Sheila Reiss Reddy: interpreted the data, contributed to the development of the manuscript, and approved the final version for publication.

Data Availability Statement

Bristol Myers Squibb policy on data sharing may be found at https://www.bms.com/researchers-and-partners/clinical-trials-and-research/disclosure-commitment.html. Data are not publicly available due to ethical reasons. Further inquiries can be directed to the corresponding author.

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