Real-world Analysis of Tyrosine Kinase Inhibitor Treatment Patterns Among Patients With Chronic Myeloid Leukemia in the United States

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ABSTRACT

Purpose: The treatment of chronic myeloid leukemia (CML) has improved considerably since the introduction of the tyrosine kinase inhibitor (TKI) imatinib in 2001 and the approval of second-generation TKIs (dasatinib and nilotinib) beginning in 2006.The objective of this study was to explore treatment patterns of TKI therapy (adherence, duration, and switching) among patients with CML in the United States, following the availability of second-generation TKIs.

Methods: This study used US health plan claims data from January 1, 2007, through December 31, 2011. Patients were required to be aged ≥18 years, have a prescription fill for a TKI, and a diagnosis of CML. Duration of TKI use was determined based on a gap in TKI coverage of ≥180 consecutive days after TKI initiation or switch to another TKI within the 180-day window. To account for censoring due to disenrollment from the health plan or end of the study period, median treatment duration was projected by using the Kaplan-Meier estimator.

Findings: We identified 695 patients who started TKI treatment and had a CML diagnosis during the study time frame. The mean age of patients was 55 years, and 58% of patients were male. The most common first-line TKI was imatinib (82%), with dasatinib and nilotinib use equally distributed (9%). Among the 148 (21.3%) patients who initiated a second-line TKI, the majority had switched from imatinib to dasatinib or nilotinib (86%). The median duration of first-line TKI use was 39.8 months and second-line TKI use was 22.4 months. Median duration of treatment for first-line ($P = 0.4342$) and second-line ($P = 0.1792$) treatment did not differ significantly according to TKI. Mean adherence (ie, proportion of days covered) during the first line of therapy was 0.90.

Implications: For the US patients studied, we found that imatinib was used more frequently than other TKIs in the first-line setting, but there was an increased use of second-generation TKIs in the first-line setting over time (9% in 2008 vs 43% in 2011 were nilotinib or dasatinib users). Only about one fifth of patients switched to a second-line TKI during the period of data collection. (*Clin Ther.* 2015;37:124–133) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key Words: adherence, chronic myeloid leukemia, duration, switching, tyrosine kinase inhibitor.

INTRODUCTION

Chronic myeloid leukemia (CML) is a hematologic cancer in which the growth of myeloid cells becomes deregulated, causing immature cells called blasts to accumulate in the blood and bone marrow.[1] CML is commonly classified into 3 stages, based on the extent of blast accumulation.[2] Patients are usually diagnosed in the chronic phase; in this phase, the disease is most mild, with <10% blasts in the blood and bone marrow. In the accelerated phase, patients typically have between 10% and 20% blasts, and the disease is more refractory to treatment. In the blast phase (ie, the most severe phase that is particularly difficult to treat), patients typically have >20% blasts, and the blasts may spread to other organs or tissues. The incidence of CML in the United States has been estimated at 1.6 cases per 100,000 individuals, and the median age of diagnosis is 64 years.[3]

Many patients with CML carry a genetic translocation referred to as the Philadelphia chromosome, in which part of chromosome 9 becomes attached to

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chromosome 22, forming the BCR-ABL fusion gene.[4] BCR-ABL is an oncogenic tyrosine kinase, and drugs that target BCR-ABL are effective in treating CML. In 2001, the tyrosine kinase inhibitor (TKI) imatinib was approved for the treatment of patients with Philadelphia chromosome–positive CML in the accelerated or blast phase or patients in the chronic phase who had failed to improve with interferon alfa therapy.[5] Shortly thereafter, in 2002, approval was expanded to the first-line treatment of CML patients in the chronic phase.[6] The second-generation TKIs dasatinib and nilotinib were initially approved as second-line therapy (in 2006 and 2007, respectively) for CML patients who had failed to improve with previous therapy, including imatinib. Dasatinib and nilotinib both subsequently received approval in the United States in 2010 for the first-line treatment of chronic phase CML.[7–10] Imatinib, dasatinib, and nilotinib are all taken orally, and response to TKIs can be measured as a hematologic response (measuring the level of blood cells), a cytogenetic response (measuring the proportion of Philadelphia chromosome–positive cells), or a molecular response (measuring the level of BCR-ABL transcripts).[11] In addition to imatinib, dasatinib, and nilotinib, the second-generation TKI bosutinib and the third-generation TKI ponatinib were approved in 2012 for the treatment of CML.[12–14]

TKI therapy has led to dramatic improvements in survival among CML patients, compared with the previous standard of interferon alfa/cytarabine therapy.[15] In the Phase III IRIS (International Randomized Study of Interferon Versus STI571) clinical study, the overall survival at 5 years among CML patients who received imatinib as initial therapy was reported at close to 90%, and at 8 years, overall survival was reported at 85%.[16,17] Although TKI therapy has provided survival benefit for many patients, there are still challenges. In the IRIS clinical study, 28% of patients discontinued therapy, and the top reasons for discontinuation were adverse events or unsatisfactory therapeutic effect.[16] Some commonly reported adverse events were edema, muscle cramps, diarrhea, nausea, musculoskeletal pain, rash/skin problems, abdominal pain, fatigue, joint pain, headache, and neutropenia. Lack of efficacy is also a problem for some patients undergoing TKI therapy, and this may result from primary or acquired resistance to TKIs. The proportion of patients who acquire drug resistance in the chronic phase is generally low (it has been reported at $\leq$25%), but resistance seems to arise more commonly among patients in the accelerated or blast phase.[16,18] Patients who acquire resistance may benefit from switching to another TKI, and the best results are typically obtained when patients switch early in the disease course (ie, during the chronic phase).[11,19–25] Patients who exhibit primary resistance or a suboptimal response to first-line TKI therapy $\leq$12 months after initiation may benefit from switching to another TKI as well.[11,26,27] Switching is also an option for patients who are intolerant to a TKI due to adverse events.[28] Choice of which second-line therapy to use can depend on the adverse event profiles of the drugs or on specific mutations in BCR-ABL (because the drugs exhibit differential activity toward particular mutations).[29] Clinical studies have found that some patients may also benefit from a third line of TKI therapy, although duration of response seems to be shorter.[30,31]

Adherence rates may also vary between the clinical trial setting and a real-world setting. Some studies have found that in an observational, or "real-world" setting, at least one quarter of patients may not be adherent to TKI therapy, and nonadherence can lead to suboptimal response or disease relapse.[32–35] Some factors that have been found to be associated with poor adherence to TKIs include adverse events, dosing considerations (eg, dosing schedule or restrictions, dosage size), a long lag time between CML diagnosis and therapy initiation, and a high number of other prescriptions.[15,32,36,37] Given the changes in the therapeutic landscape for CML over the past decade, particularly the availability of the initial second-generation TKI inhibitors starting in 2006 and 2007, the present study was performed to investigate (by using medical claims data) recent treatment patterns among CML patients in the United States. The study design offers a different perspective from clinical trials, and is able to provide insight into CML treatment patterns in a real-world setting. The objective of the present study was to examine real-world therapy duration and switching among patients with CML. We also compared real-world TKI therapy duration with that observed in a clinical trial setting.

PATIENTS AND METHODS

Data Source

This study was an observational, retrospective analysis using medical and pharmacy claims data and linked enrollment information from patients in a large managed health care plan. Underlying