Original Study

The Effectiveness of Tyrosine Kinase Inhibitors and Molecular Monitoring Patterns in Newly Diagnosed Patients With Chronic Myeloid Leukemia in the Community Setting

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Abstract

Little evidence exists to evaluate the effectiveness of first-line tyrosine kinase inhibitors in the community setting. Through electronic health records, 300 chronic myeloid leukemia patients were identified. Similar to clinical trials, dasatinib and nilotinib had higher cytogenetic and molecular responses and faster molecular responses than imatinib in a community setting. Frequency of response monitoring was lower than recommended in the guidelines.

Background: Clinical outcomes of patients with chronic myeloid leukemia (CML) treated in clinical trials, including response to therapy, may not be representative of those treated in a community setting. Thus, we sought to determine the real-world effectiveness of first-line tyrosine kinase inhibitors in CML by evaluating response rates, all-cause discontinuation, and adherence. Response monitoring patterns were also analyzed. **Patients and Methods:** This retrospective observational study, using the McKesson Specialty Health/US Oncology Network (MSH/USON) iKnowMed electronic health record database and medical charts, identified newly diagnosed CML patients who received first-line imatinib, dasatinib, or nilotinib from July 2007 to March 2011, and were then followed for $\geq$ 18 months. **Results:** Three hundred patients met study criteria (222 imatinib-treated, 34 dasatinib-treated, and 44 nilotinib-treated in the first-line). Molecular and cytogenetic response assessments were conducted less frequently than recommended (40% never had cytogenetic or molecular monitoring at any time). Patients treated with either dasatinib or nilotinib experienced higher response rates by 6, 12, and 18 months, faster time to major molecular response, and a significantly lower rate of all-cause treatment discontinuation within 18 months relative to imatinib-treated patients. Approximately 56% of all patients were adherent to tyrosine kinase inhibitor therapy. **Conclusion:** Dasatinib and nilotinib were more effective than imatinib as first-line therapy for CML in a community setting, as observed in descriptive and univariate analyses. The frequency of cytogenetic and molecular monitoring was lower than that recommended by current guidelines, including patients with no molecular or cytogenetic assessments during the 18-month follow-up. Therefore, MSH/USON is working toward improving compliance with response monitoring guidelines.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■ © 2015 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Keywords: Adherence, Dasatinib, Frequency of response assessments, Imatinib, Nilotinib

Presented in part at the 55th Annual Meeting of the American Society of Hematology, in December 2013.

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Submitted: Mar 17, 2015; Revised: Jun 1, 2015; Accepted: Jun 12, 2015

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http://dx.doi.org/10.1016/j.clml.2015.06.006

Introduction

Tyrosine kinase inhibitors (TKIs) have revolutionized the treatment of chronic myeloid leukemia (CML), dramatically improving the prognosis of treated patients.[1-8] Three TKIs are currently approved for first-line treatment of CML in the chronic phase (CML-CP): imatinib, dasatinib, and nilotinib.[9-11] Imatinib was the first TKI approved for the treatment of newly diagnosed patients with CML-CP[9]; however, resistance and intolerance account for a significant number of patients unable to continue treatment.[1,12] The second-generation TKIs dasatinib and nilotinib were then developed to treat patients with CML-CP in whom imatinib therapy had failed.[10,11]

In the DASISION (Dasatinib vs. Imatinib Study in Treatment-Naive CML Patients) trial, dasatinib showed superior efficacy over imatinib in newly diagnosed patients with CML-CP, leading to its first-line approval.[2-4,10] Specifically, the rate of confirmed complete cytogenetic response (CCyR) by 12 months was significantly higher with dasatinib than with imatinib (77% vs. 66%, $P = .007$), as was the rate of major molecular response (MMR) by 12 months (46% vs. 28%, $P < .0001$).[2] For dasatinib versus imatinib, median time to MMR was faster with dasatinib (9.2 vs. 15.0 months).[4] Nilotinib was also approved for the first-line treatment of patients with CML-CP based on the results of the ENESTnd (Evaluating Nilotinib Efficacy and Safety in Clinical Trials—Newly Diagnosed Patients) trial.[6-8,11] At 12 months, the rates of MMR for 2 dose levels of nilotinib (300 mg and 400 mg twice daily) were higher than that for imatinib (44% and 43% vs. 22%, respectively; $P < .001$ for both comparisons), and the rates of CCyR by 12 months were higher with nilotinib as well (80% and 78% vs. 65%, respectively; $P < .001$ for both comparisons).[6] Median time to MMR was also faster for nilotinib (8.3 months) compared with imatinib (11.1 months).[7]

Response monitoring is critical to the management of CML-CP in order to identify patients with suboptimal response or resistance to TKI therapy. The current response monitoring recommendations from the National Comprehensive Cancer Network (NCCN) CML guidelines support molecular testing via quantitative real-time polymerase chain reaction (qPCR) using the International Scale (IS) every 3 months for patients responding to treatment, every 3 months for 3 years once CCyR has been achieved, and then every 3 to 6 months.[13] Bone marrow cytogenetics are recommended at 3 and 6 months if qPCR is not available, at 12 months if CCyR or MMR are not achieved, and at 18 months if the patient had not previously achieved CCyR or MMR at 12 months.[13] European LeukemiaNet (ELN) guidelines similarly recommend frequent monitoring.[14]

Molecular monitoring as recommended by the current guidelines is also associated with increased adherence to TKI therapy, and this may have significant clinical implications.[15] Adherence to TKIs is essential for the achievement of durable hematologic, cytogenetic, and molecular responses. In clinical studies of imatinib-treated patients, nonadherence has been shown to contribute to the failure to achieve CCyR, MMR, and complete molecular response.[16,17] However, there is a lack of quantitative information available regarding adherence to TKI therapy and its association with clinical response in the community setting.

Patients who are appropriately monitored outside of clinical trials may have similar outcomes to those enrolled in trials[18]; however, monitoring in the community setting appears to be less frequent than guidelines recommended by the NCCN and ELN.[19-22] In the present analysis, the effectiveness of first-line TKIs was investigated in community-based oncology practices. Specifically, we evaluated response rates, adherence, and all-cause discontinuation in patients with CML. Response monitoring patterns were observed as well. This study also attempted to provide the groundwork for future comparative effectiveness assessment among the 3 TKIs, with further accrual of patients treated with second-generation TKIs in clinical practice.

Patients and Methods

Patient Population

CA180-508 is a retrospective observational cohort study of patients with CML treated with imatinib, dasatinib, or nilotinib in the first-line setting in the community clinical practices of the McKesson Specialty Health/US Oncology Network (MSH/USON). Patients receiving care at an MSH/USON site between July 1, 2007, and March 31, 2011, were evaluated for enrollment criteria.

Patients were eligible for inclusion in the study if they were more than 18 years old and newly diagnosed with CML, received a TKI as first-line therapy, received care at an MSH/USON practice using full iKnowMed electronic health record (iKM EHR) capabilities, and had more than 1 visit recorded during the study period. Only patients with CML-CP were included in the response analyses. Patients were excluded from the study if they were enrolled in clinical trials during the study period or if they were diagnosed with or treated for other cancers.

Patients were followed for $\geq$ 18 months from the date of enrollment, and data collected as of September 30, 2012, are analyzed in the present report. Data were extracted using programmatic query of MSH/USON's iKM EHR system, electronic medical record chart review, and the Social Security Death Master File.

Definitions

Complete hematologic response was defined as average leukocyte count $< 10 \times 10^9$/L, average platelet count $< 450 \times 10^9$/L, and average myelocyte, promyelocyte, and blast count in peripheral blood = 0 or missing during 0 to 3, 4 to 6, and 7 to 12 months of follow-up. CCyR was defined as absence of Philadelphia chromosome–positive metaphases as measured by bone marrow cytogenetics, or < 1% *BCR-ABL*-positive nuclei by fluorescence in-situ hybridization. MMR was defined as $\geq$ 3-log reduction of *BCR-ABL* mRNA transcripts from baseline, or *BCR-ABL* $\leq$ 0.1% on the IS.

Adherence to TKI therapy was estimated as actual days of TKI therapy divided by total days of recommended therapy, converted to a percentage, using physician prescription records. Data on prescription fills and actual use of drug were not available. Patients were considered adherent if they had $\geq$ 90% adherence.

Progression was defined as the occurrence of bone marrow transplant, transformation to accelerated phase (AP) or blast phase (BP), or death.

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