Monitoring Chronic Myeloid Leukemia in the Real World: Gaps and Opportunities

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Abstract

In clinical trials, in which treatment algorithms and monitoring schedules are tightly prescribed by research protocols, outcomes for patients with chronic myeloid leukemia (CML) have been excellent, with > 90% 5-year survival rates. However, outside of clinical trials in the so-called real world, monitoring schedules are more variable, with < 40% of patients undergoing quantitative polymerase chain reaction (qPCR) molecular testing 3 to 4 times during the first year after diagnosis as recommended by National Comprehensive Cancer Network/European Leukemia Net (NCCN/ELN) evidence-based guidelines. Results from chart reviews, claims-based databases, and observational databases suggest that carefully monitored patients with CML are more likely to be adherent to medications, incur fewer hospitalizations, experience lower overall treatment costs, and have better progression-free survival and overall survival compared with patients who are not monitored. Regular monitoring provides valuable early information on treatment responses that physicians can use to modify treatment. Unfortunately, physician-perceived resource barriers, lack of familiarity, and lack of agreement have restricted monitoring guideline adoptions. Multifaceted approaches to encourage appropriate monitoring are needed to improve clinical outcomes and reduce costs in the real world.

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Introduction

There are 3 key elements to successful treatment of the patient with chronic myeloid leukemia (CML) in the chronic phase: (1) availability of effective medications, (2) adherence by the patient to the therapeutic regimen, and (3) appropriate monitoring of treatment response by the physician. The oral tyrosine kinase inhibitors (TKIs) have revolutionized the medical management of CML and satisfy the first criterion. With imatinib, nilotinib, and dasatinib, > 70% of patients can expect to achieve a complete cytogenetic remission, and 20% to 40% will demonstrate suppression of Bcr-Abl transcript levels leading to a major molecular response (< 0.1% on the international scale) by the end of the first year of treatment.[1-3] Thus, using these effective medications, patients with CML enrolled in clinical trials have achieved 5-year survival rates exceeding 90%.

Patients must also take their oral TKI regimens over protracted time frames. Unfortunately, nonadherence has been shown to be a problematic area for patients with CML. Based on medication possession ratio (MPR) thresholds, between 40% and 64% of patients with CML are nonadherent to first-line therapy, and only 14% to 50% are fully adherent.[4-8] A blinded survey of 88 patients with CML at the John Theurer Cancer Center revealed by self-reporting that 25% had not taken all their medications during the previous 3 months, with young patients (< 50 years) being less likely to be adherent ($P = .004$). Forgetfulness was the most common reason for missing doses, followed distantly by side effects and financial reasons.[9] The clinical implications of nonadherence can be significant, with patients who miss 10% of their daily doses (ie, 3 days per month) having a lower likelihood of achieving a major molecular response and a higher likelihood of loss of cytogenetic response.[10,11] Because nonadherence is a common issue, National Comprehensive Cancer Network (NCCN) CML guidelines recommend that when patients fail to achieve optimal response at specific milestones, physicians first assess patient adherence before making any treatment adjustments.[12]

Appropriate monitoring of response to TKI therapy by the treating physician is the third key element to successful outcomes. In clinical trials, monitoring of participants is tightly prescribed by the research protocol. To assist in the care of patients with CML in the real world, the NCCN and European LeukemiaNet (ELN) have each published (and regularly update) recommendations on monitoring based on level 2A (expert consensus) evidence.[12,13] Since 2006, the guidelines have recommended quarterly monitoring by polymerase chain

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reaction (PCR) technology during the first year after diagnosis. However, are these monitoring guidelines followed outside of research settings, and if not does this alter clinical outcomes?

Rates of Monitoring CML in the Real World

Case Report Reviews

Case report reviews have noted considerable undermonitoring of newly diagnosed patients with CML compared with the published guidelines (NCCN or ELN). For example, 38 community-based oncologists throughout the United States submitted reports on 402 patients with CML receiving first-line therapy with imatinib.[14] The physicians participating in this review were experienced in treating CML, with 76% actively providing medical care for more than 10 patients with CML. During the first 3 years of treatment, the chart review documented that 13% of patients did not undergo any molecular monitoring, 40% underwent 1-2 tests per year, and only 46% met guideline recommendations of 3-4 tests per year. Interestingly, the lack of testing was not limited to a few physicians. Half of the physicians had at least 1 patient in the 0 tests per year group, suggesting that the physicians were selective in whom they chose to monitor. It was noted that the monitored versus unmonitored groups had similar distributions of age, smoking status, insurance type, and comorbidities, although African-Americans were more likely to be monitored than were whites. Of the 209 patients in whom the Sokal score was calculated, the high-risk patients were monitored at the same rate as the low-risk patients. However, among the 366 patients whose spleen size was measured, it was found that more patients who had an enlarged spleen underwent monitoring. Thus, it is possible that the visible signs of cancer (ie, a large spleen) may have triggered the physician to believe that the patient was at higher risk and therefore needed closer monitoring. These results were in agreement with a second chart review involving 297 patients that noted that 21% of these patients never underwent molecular monitoring in the first 18 months of therapy, and only 39% of patients received regular quantitative PCR (qPCR) testing every 3-6 months.[15]

Database Reviews

Administrative claims databases permit retrospective analysis of practice patterns over large population-based cohorts. Again, using these data sources, undermonitoring was identified. A total of 1205 patients with newly diagnosed chronic-phase CML were identified in a retrospective review of the IMS LifeLink Health Plan Claims database and the Truven Health Analytic MarketScan (covering > 80 million lives annually throughout the United States) between 2007 and 2012.[16] At presentation, 52% of the patients were men, the mean age was 54 years, and 90% received first-line imatinib therapy. During the initial 12 months after diagnosis, 41% of the patients underwent no qPCR monitoring, 32% had 1-2 tests, and only 27% underwent the NCCN/ELN guideline—recommended 3-4 tests per year. The unmonitored patients were slightly older (57 years vs. 53 years vs. 51 years, respectively; $P < .01$) and had more cardiovascular comorbidities, including hypertension, but had lower CML complexity scores ($P < .05$; based on an algorithm used to determine the difficulty in managing a patient based on comorbid conditions).[6]

Observational databases permit an in-depth assessment of practice patterns, potentially on a prospective basis.[17] The World CML Registry is collecting data on 1837 patients receiving first-line CML therapy. Of 1083 patients in whom an assessment was available at 3 months, only 10% underwent cytogenetic testing and only 15% underwent molecular testing. By 6 months, the rates of cytogenetic and molecular testing both rose to 39%. At 1 year, among the 931 patients followed in the registry, only 38% had undergone a cytogenetic test and 50% had undergone a molecular PCR test to follow their disease.[18] A subgroup analysis of 193 evaluable patients from the United States in this registry who were followed for at least 1 year found similar undermonitoring, with only 32% and 51% undergoing cytogenetic or molecular studies, respectively.[19]

SIMPLICITY is an ongoing observational study of CML being conducted in 7 countries and involving 220 sites. The prospective treatment arms have enrolled > 1200 patients newly diagnosed with CML and receiving first-line therapy with either imatinib, dasatinib, or nilotinib.[20] As of April 2014, 862 patients had been followed for a minimum of 1 year, with two thirds of patients (n = 573) being followed in the United States and one third in Europe (n = 289). In the United States, the majority of patients were treated in community settings (370 community practices vs. 203 academic institutions), whereas in Europe the majority of patients are followed in academic centers (225 academic institutions vs. 64 community practices). The median age of patients in this observational database was 55 years and was statistically higher in the imatinib cohort (age 59 years) compared with the cohort receiving second-generation agents. Among the patients followed for 1 year, 49% had undergone at least 1 cytogenetic monitoring evaluation, and 83% had undergone at least 1 molecular monitoring test. The rate of testing was similar between American and European sites. Overall, only 37% of the patients underwent 3-4 molecular tests during the first year as recommended by the NCCN/ELN guidelines (41% in Europe and 36% in the United States). The rates of cytogenetic testing in the first 12 months of follow-up were higher at academic centers than in community practices (58% vs. 39%; $P < .001$). However, the difference in molecular testing was less pronounced between practice settings, with 87% of patients tested in academic centers compared with 79% at community centers. Overall, 10% of patients at academic centers were not tested for either cytogenetic or molecular markers compared with 14% of patients in community practices.

Does Monitoring Matter?

As already noted, less than half of patients with CML outside of clinical trials are monitored according to published (NCCN or ELN) guidelines. Is this because physicians in the real world do not find monitoring to affect outcomes? Unfortunately, the data demonstrate just the opposite; unmonitored patients experience inferior outcomes.

Case Report Reviews

In the case report study described earlier involving 402 patients treated with first-line imatinib and followed by 38 community physicians, it was found that there was a higher rate of disease progression (hazard ratio, 0.085; $P = .001$) and a shorter progression-free survival (hazard ratio, 0.088; $P = .001$) if molecular monitoring did not follow guideline recommendations (after adjusting for potential