Study: CML Monitoring Guidelines Not Consistently Followed in Community Setting

BY HEATHER LINDSEY

Patients with chronic myeloid leukemia (CML) who are receiving care in a community setting may not be undergoing the proper amount of cytogenetic and molecular monitoring to assess their response to tyrosine kinase inhibitors (TKIs). That is the conclusion of a study published in *Clinical Lymphoma, Myeloma & Leukemia* (***2015;15:599-605***).

The results showed that molecular and cytogenetic response assessments were conducted less frequently than recommended by the National Comprehensive Cancer Network in patients with chronic-phase CML—"which was surprising," said the study's lead author, Nicholas J. Di Bella, MD, a hematologist at Rocky Mountain Cancer Centers in Aurora, Colorado and the McKesson Specialty Health/US Oncology Network in The Woodlands, Texas.

"This was an eye opener for us, and a matter of concern. The main reason for reporting these data was that we felt that community physicians need to be following these guidelines more closely."

'Amazingly Low Compliance Rate to Medication'

While the researchers found that the overall effectiveness of TKIs in patients treated in the community reflected that found in previous clinical trials, patients had "an amazingly low compliance rate" to medication, Di Bella said.

Still, despite the troubling findings of this report, TKI therapy for newly diagnosed CML patients in actual clinical practice remained highly successful, which was reassuring, commented Eunice Wang, MD, Chief of the Leukemia Service and Associate Professor of Oncology and Assistant Member of the Tumor Immunology Program at Roswell Park Cancer Institute in Buffalo.

Also asked for her perspective for this article, Maen Hussein, MD, a medical oncologist at Florida Cancer Specialists and a member of the Advisory Committee for the Association of Community Cancer Centers' 2010-2011 project on CML, said: "Overall, I don't think community oncologists are lacking. As the study demonstrated, patients were experiencing good response rates, regardless of monitoring.

Study Details

Using electronic medical records and medical charts, the researchers conducted a retrospective, observational cohort study of 300 chronic-phase CML patients who received first-line imatinib, dasatinib, or nilotinib in community clinical practices at the McKesson Specialty Health/US Oncology Network from July 2007 to March 2011.

Patients were followed for at least 18 months. Overall, 222 received imatinib, 34 had dasatinib, and 44 had nilotinib.

During the time period observed, 40 percent of patients did not receive genetic or molecular monitoring. Seventy-six percent did not receive both a cytogenetic and molecular response assessment. Molecular monitoring frequency fluctuated, with 18 percent of individuals assessed at 13 to 18 months, ranging from 30 percent of patients tested at seven to 12 months and 18 percent tested at 13 to 18 months.

Eighty-nine percent of CML patients treated with first-generation imatinib and 94 percent of patients treated with either second-generation dasatinib or nilotinib achieved a complete hematologic response at four to six months; at seven to 12 months, these rates were 84 and 82 percent, respectively.

For individuals who did undergo cytogenetic or molecular testing, the cumulative response rates as indicated by these tests increased for both imatinib and second-generation TKIs. However, the rates were higher in patients who took dasatinib or nilotinib versus imatinib at six, 12, and 18 months.

For example, 61 percent of individuals taking a second-generation TKI achieved a cytogenetic or molecular response by 12 months versus 38 percent of those taking imatinib. Time to a major molecular response was significantly faster in patients treated with a second-generation TKI compared with those receiving imatinib.

Dasatinib and nilotinib were more effective than imatinib as first-line therapy for CML in a community setting, as observed in prior clinical trials, which was to be expected, since dasatinib and nilotinib are more potent TKIs, Di Bella noted.

The time to discontinuation was significantly longer for patients treated with second-generation TKIs than for those receiving imatinib.

Adherence was estimated as the actual days of TKI therapy divided by the total days of recommended treatment, converted to a percentage. The researchers considered 90 percent or higher as adherent.

Adherence rates were 56 percent in the imatinib group and 55 percent in the second-generation TKI group.

Time Factor

Hussein noted that while the findings may motivate community oncologists to look at the issue of guideline adherence more closely, the timing of the study may not reflect how physicians are currently practicing.

"In 2007, not many of us had an EMR. When these systems were first introduced, doctors may not have been routinely documenting how they were practicing. Moreover, documents from other care providers may not have been regularly scanned into the EMR."

In 2007, oncologists also had less of an understanding of how to best monitor CML because of the relative newness of TKIs—whether it was with complete blood counts or polymerase chain reaction (PCR), which was not easy to order at the time, Hussein added. "It takes time to adapt guidelines into clinical practice."

Challenges

Wang said that the study results clearly demonstrated that the importance of performing monitoring tests has not been conveyed to the majority of community practitioners.

Di Bella said several challenges can interfere with adherence to monitoring guidelines. For example, in some practices, one physician may be managing many different types of cancer and may not be particularly interested in following the specifics for hematologic malignancies: "It's becoming increasingly challenging for oncologists to keep up with all the advances in treatment and monitoring," he said.

In practices with at least four to five oncologists, having one physician dedicated to treating hematologic

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FDA's Breakthrough Therapy & Orphan Drug Designations to Drug for Tenosynovial Giant Cell Tumor

The U.S. Food and Drug Administration has granted Breakthrough Therapy and Orphan Drug designation to pexidartinib (formerly PLX3397) for the treatment of tenosynovial giant cell tumor (TGCT) where surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity. Pexidartinib is an investigational oral small molecule that potently and selectively inhibits colony-stimulating factor-1 receptor (CSF-1R).

The Breakthrough Therapy designation, enacted as part of the FDA's 2012 Safety and Innovation Act, was created to expedite the development and review time of a potential new drug for serious or life-threatening disease where early clinical evidence suggests the drug may demonstrate substantial improvement compared with existing therapies.

The Orphan Drug designation—to encourage development of drugs in the diagnosis, prevention, or treatment of a medical condition affecting fewer than 200,000 people in the U.S.—grants a product market exclusivity for a seven-year period if the sponsor complies with certain FDA specifications, as well as tax credits and prescription drug user fee waivers. The designation does not, though, shorten the duration of the regulatory review and approval process.

Currently, there is no FDA-approved systemic therapy for the treatment of TGCT, notes a news release from Daiichi Sankyo, Inc., and Plexxikon Inc., who are developing the drug.

The designations for pexidartinib were granted based on results from an extension cohort of a single-arm, multicenter Phase I study that assessed the safety and efficacy of pexidartinib, which provided the proof-of-concept that selective CSF-1R inhibition with pexidartinib may safely and effectively reduce tumor burden in patients with TGCT.

The Phase III study of pexidartinib, called ENLIVEN, is currently enrolling patients with symptomatic TGCT for whom surgical removal of the tumor would be associated with potentially worsening functional limitation or severe morbidity.

The most common treatment-related adverse events seen in the ongoing Phase I study of pexidartinib included fatigue, hair color changes, nausea, dysgeusia, and periorbital edema. Treatment-related severe adverse events included fatigue, diarrhea, anemia, hyponatremia, elevated liver enzymes, and neutropenia.

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malignancies would be ideal, but is not always feasible, Di Bella said.

Also asked for his perspective, Jack Jacoub, MD, Medical Director of Orange Coast Blood & Cancer Care and Director of Thoracic Oncology at MemorialCare Cancer Institute at Orange Coast Memorial Medical Center in Fountain Valley, California, said that physicians also need to recognize that while sharing information with patients about the efficacy of CML medications, "this assurance can be a double-edged sword. Patients assume that they will do well, regardless of whether or not they are monitored and attend appointments."

> "The McKesson Specialty Health/US Oncology Network is now working toward improving compliance with response monitoring guidelines."

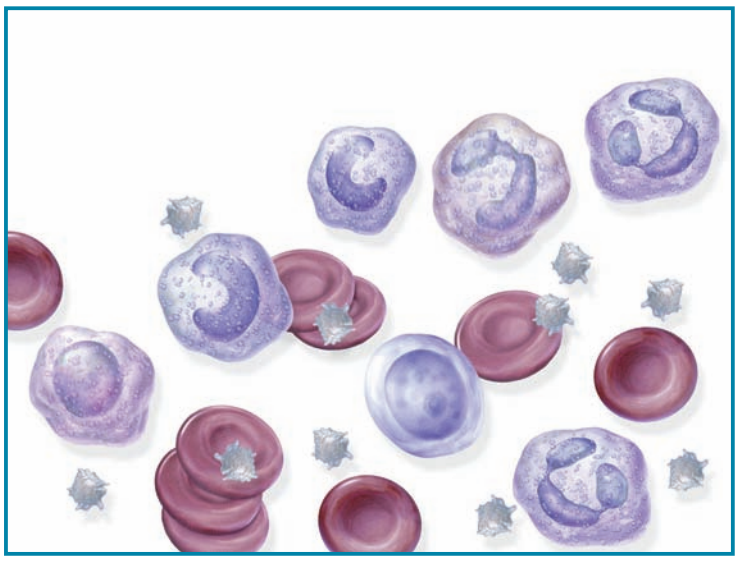
In addition, Jacoub said, in some cases, patients who do well for many years and over decades may stop receiving care at a specialty center and then see a primary care physician, who may not be aware of monitoring guidelines. Because CML is a long-term disease, the intensity of follow-up may thus wane over time.

Physician and Patient Education

Physicians need to be aware that adhering to guidelines of monitoring and adjusting therapy accordingly may improve overall outcomes, Jacoub said.

Di Bella noted that there is still a debate about whether to start patients on imatinib or second-generation TKIs. "However, if you're monitoring patients on imatinib at appropriate intervals and the CML is not responding, it's easy to switch to another TKI." The critical factor is to be monitoring serial measurements to make an informed decision.

He noted that he and his colleagues have added reminders in the EMR system to alert physicians about the need to conduct molecular and cytogenetic monitoring tests in newly diagnosed CML patients at three, six, nine, and 12 months.



The researchers are considering conducting a prospective analysis of their centers' monitoring activities now that they have EMR reminders in place.

Oncologists also need to ensure that their patients and caregivers understand the significance of testing and the milestones in the treatment of chronic-phase CML, said Pamela Crilley, DO, Chair of the Department of Medical Oncology at Cancer Treatment Centers of America and Chief of Medical Oncology at the Eastern Regional Medical Center in Philadelphia.

In addition to being aware that laboratory testing needs to occur at three-month intervals, patients need to understand that the treatment goal is to achieve a complete hematologic response first, followed by a complete cytogenetic response, ideally within the first 12-month period. Following that, the goal is to achieve a major molecular response, which can be assessed by PCR testing, she said.

Addressing the Problem

Adherence and its impact on outcomes needs to be addressed with any chronic illness in which patients are asked to take daily medications indefinitely, Jacoub emphasized.

And, Di Bella noted, many patients have difficulty following a routine and taking drugs regularly. However, if patients know that the success of treatment depends on adherence, they will be more likely to comply.

Oncologists may be able to improve the TKI compliance rate by taking a more active role in educating patients, both verbally and in writing, at each clinic visit, Wang concluded.

Providing patient diaries and enlisting the help of a nurse educator, pharmacist, or family member to reinforce instructions may also be beneficial.