VIEWPOINT

Ibrutinib's Cardiotoxicity—An Opportunity for Postmarketing Regulation

Mark J. Ratain, MD
Section of Hematology/Oncology, Department of Medicine, The University of Chicago, Chicago, Illinois; and Value in Cancer Care Consortium, Ann Arbor, Michigan.

Javid J. Moslehi, MD
Division of Cardiovascular Medicine, Department of Medicine, Vanderbilt University, Nashville, Tennessee.

Allen S. Lichter, MD
Value in Cancer Care Consortium, Ann Arbor, Michigan.

Ibrutinib is an irreversible inhibitor of Bruton tyrosine kinase (BTK) that is indicated for multiple hematological malignancies, including previously untreated chronic lymphocytic leukemia (CLL). This drug is known to have cardiotoxic properties, probably due to off-target inhibition of another kinase. While in randomized trials ibrutinib has been demonstrated to increase survival, some studies have demonstrated fatal toxic effects associated with the drug. This was most obvious in a 3-arm study of CLL in which the 2 ibrutinib arms were associated with a 7% rate of death during treatment or within 30 days after treatment cessation, compared with a 1% rate of death in the control arm.[1]

Similar toxicity has not yet been as prominent for acalabrutinib, another BTK inhibitor approved in November 2019, although the acalabrutinib package insert includes a warning regarding the risk of atrial fibrillation and flutter.

The recent analysis of real-world data from the World Health Organization's VigiBase (a registry of individual case safety reports from >130 countries)[2] should have set off alarm bells at the US Food and Drug Administration (FDA). This analysis included 13 572 reports involving ibrutinib as of January 2018, primarily in patients receiving treatment for CLL. More than 97% of the events were from 2015-2017 and included 303 ibrutinib-associated deaths. Of total deaths, 103 were due to arrhythmias, and 90 were due to central nervous system hemorrhage. Conduction disorders (mainly high-grade atrioventricular block) were also notable. This previously unreported adverse event occurred as early as the first dose (median time of onset was 27.5 days) and had an 18% mortality rate (9 deaths). The median age of patients who died was in the low 70s, somewhat older than the clinical trial populations, reflecting the real-world experience seen with most cancer drugs as they move from tightly controlled clinical trials into the broader patient population.

This increased rate of serious complications and death may be caused, in part, by an unnecessarily high dose of the drug having been approved by global regulatory agencies and thus prescribed for multiple indications by hematologists and oncologists worldwide. Ibrutinib first received FDA approval in 2013 for the treatment of mantle cell lymphoma at a dosage of 560 mg/d based on a small phase 1 study.[3] Since then it has received approval for multiple other indications at a dosage of 420 mg/d, including CLL, Waldenstrom macroglobulinemia, marginal zone lymphoma, and chronic graft-vs-host disease.

While multiple issues may contribute to ibrutinib's toxicity, we hypothesize that a much lower dose would have a superior therapeutic index. In the FDA's 2013 review of the original new drug application, it was noted that the target saturation peaked at about 2.5 mg/kg and remained flat in the face of increasing dose.[4] Yet Pharmacyclics applied for and received approval for a labeled dosage of 560 mg/d (approximately 8 mg/kg) in its original application, and 420 mg/d (approximately 6 mg/kg) in subsequent applications. In analyzing the original application, the FDA reviewers included the following comment to the sponsor: "We recommend you evaluate lower doses in future clinical development as data from the phase 1 trial PCYC-04753 showed that maximum BTK occupancy and maximum response were achieved at doses of ≥2.5 mg/kg."[4]

Two additional pieces of evidence supporting the FDA's suggestion are worth noting. A small study from MD Anderson Cancer Center[5] used sequential dose reduction from 420 mg to 280 mg to 140 mg, without any loss of BTK binding. There was also no evidence of any loss of antileukemic effect, although this was only a pilot study for which 9 patients completed the 2 sequential dose reductions. Notably, the off-target effect on platelet aggregation was reduced at the lower doses. In addition, a recent report from Mayo Clinic[6] looked at 209 patients with CLL who were treated with ibrutinib. A starting dosage of 420 mg/d was used in 122 patients, 280 mg/d was used in 35 patients, and 52 patients received 140 mg or less per day. Event-free and overall survival appeared to be independent of starting dose.

Despite the FDA recommendations for further testing at lower doses, no additional studies have been performed by the manufacturer. The FDA could have required that such a study be conducted at the time of the original approval in 2013 or in the context of subsequent approvals for additional indications and formulations. Furthermore, under the FDA Amendments Act of 2007, the agency has the authority to require additional studies at any time to assess a known serious risk related to the use of any drug.[7]

The considerations with respect to appropriate clinical dose become more relevant given the emerging data regarding the cardiotoxicity associated with ibrutinib.[2] A 2019 preclinical study[8] that tested the effects of ibrutinib on stem cell–derived cardiomyocytes differentiated into "atrial-like" cardiomyocytes found that ibrutinib caused a dose-dependent decrease in action potential duration and cardiomyocyte viability that was associated with an increase in calcium transient duration. These preclinical results are consistent with recent evidence regarding the serious cardiac adverse events associated with ibrutinib use.[2]

It is unclear if a lower dose will mitigate the cardiovascular death rate; susceptible patients may have the same adverse outcome regardless of dose. Neverthe-

Corresponding Author: Mark J. Ratain, MD, Department of Medicine, The University of Chicago, 5841 S Maryland Ave, MC 2115, Chicago, IL 60637 (mjr1@uchicago.edu).

less, it would be important to find out. A study comparing the labeled dosage (420 mg/d) to lower dosages known to be effective (140 mg/d and 280 mg/d) would settle the question. If, with a lower dose, the drug's toxicity is not decreased or efficacy is decreased, we can continue to use as carefully as possible the current labeled dose. But if a study shows that a lower dose works as well and reduces its toxicity, we have positively changed the lives of tens of thousands of patients who use this drug. It is time for the FDA to require such a study and for the manufacturer to carry it out expeditiously. Given the high efficacy of ibrutinib and other BTK inhibitors, there is no reason to expose patients with an expected survival of many years to unnecessary cardiac risks attributable to an excessive dose of ibrutinib.

While other BTK inhibitors may have a superior therapeutic index to ibrutinib at its labeled dose, there is no evidence that these newer BTK inhibitors are fully interchangeable with ibrutinib, particularly as the approved indications across this class of drugs vary by drug. Furthermore, it is unknown what off-target events will emerge as the newer BTK inhibitors are more widely used. It is also not known whether reversible BTK inhibitors in development will have the same efficacy as the current drugs. This is a case in which the accumulation of real-world data makes FDA postmarketing regulation critically important. One could argue that a randomized dose-ranging study of ibrutinib should have been mandated years ago, but under the FDA Amendments Act of 2007, the agency has the authority to require this study now and should do so.

ARTICLE INFORMATION

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