The promised land

Eytan M. Stein

Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA

E-mail: EYTAN M. STEIN - steine@mskcc.org

doi:10.3324/haematol.2020.276428

In 2021, most, if not all, presentations and publications about the treatment of acute myeloid leukemia (AML) start biblically: hematologists spent 40 years in the desert of "7+3" and in 2017 reached a promised land flowing with Food and Drug Administration approvals. One of the first approvals addressed the vexing problem of *FLT3*-mutant AML. While the *FLT3*-internal tandem duplication (ITD) was discovered over 25 years ago, the success of randomized clinical studies targeting the mutant FLT-3 protein only occurred years later with the RATIFY trial.[1] In this trial, the combination of the multikinase inhibitor midostaurin with induction chemotherapy led to a statistically significant improvement in the 4-year overall survival of patients with newly diagnosed *FLT3*-mutant AML.[2] The approval of single-agent gilteritinib, a second-generation FLT-3 inhibitor for patients with relapsed and refractory AML, based on the randomized phase III ADMIRAL trial, consolidated the role of FLT-3 inhibitors in the treatment of patients with AML.[3]

But while gilteritinib was being approved, a second FLT-3 inhibitor, quizartinib, was axed by the Oncologic Drugs Advisory Committee (ODAC). Quizartinib, a potent inhibitor of *FLT3*-ITD but not *FLT3*-tyrosine kinase domain (TKD) mutations, was studied in a randomized phase III trial, for relapsed and refractory AML. Despite demonstrating a statistically significant overall survival benefit in the company-sponsored analysis of the clinical trial, concerns about dropouts in the standard treatment arm led to a negative vote against quizartinib at an ODAC meeting. Despite this, quizartinib was approved in Japan and is now a standard-of-care therapy in that country.

Building on previous work showing the relative benefit of treating patients with the combination of sorafenib, a weak FLT-3 inhibitor, with azacitidine, in this issue of *Haematologica*, Swaminathan and colleagues[4] report the outcomes of patients with either newly diagnosed or relapsed *FLT3*-ITD AML treated with the combination of azacitidine or low-dose cytarabine with quizartinib. Perhaps the most impressive outcome in this trial is the high rate of composite complete response of 87% with quizartinib/azacitidine and 74% with quizartinib/low-dose cytarabine. These rates of remission are certainly encouraging, although definitive results will need to wait for the time of a randomized, ideally placebo-controlled, study. As a cautionary note, the randomized phase III LACEWING study, in which patients were assigned to treatment with the two-drug combination of gilteritinib/azacitidine or azacitidine monotherapy, failed to meet its primary endpoint of an overall survival benefit in favor of the former despite encouraging results of the "doublet" in a phase II clinical trial.

Concurrent with the development of treatments targeting FLT-3, there has been a dramatic improvement in the outcomes of adults who are not considered good candidates for induction chemotherapy with the use of azacitidine and venetoclax. *FLT3*-mutant patients appear to do as well with azacytidine/venetoclax as patients without *FLT3* mutations, at least when it comes to response. How then, should we think about the doublet of azacitidine/quizartinib? The field of leukemia research is now moving past doublets, and Swaminathan and colleagues have set a firm foundation for thinking about triplets of azacitidine/venetoclax/quizartinib or sequential treatments with azacitidine/venetoclax followed by azacitidine/quizartinib. Studies on these combinations will take time to perform but are worthwhile and will continue to improve the lives of all of our patients with *FLT3*-mutant AML.

Disclosures

No conflicts of interest to disclose.

References

1. Nakao M, Yokota S, Iwai T, et al. Internal tandem duplication of the flt3 gene found in acute myeloid leukemia. Leukemia. 1996;10(12):1911-1918.
2. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.
3. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381(18):1728-1740.
4. Swaminathan M, Kantarjian HM, Levis M, et al. A phase I/II study of the combination of quizartinib with azacitidine or low-dose cytarabine for the treatment of patients with acute myeloid leukemia and myelodysplastic syndrome. Haematologica. 2021;106(8):2121-2130.