

Venetoclax safe, shows promise in patients with acute myelogenous leukemia

August 15 2016

Patients whose acute myelogenous leukemia (AML) had relapsed or was resistant to chemotherapy and those who were deemed unable to tolerate chemotherapy experienced responses to the selective BCL-2 inhibitor venetoclax (Venclexta), with complete remissions in some, according to phase II clinical trial data published in *Cancer Discovery*, a journal of the American Association for Cancer Research.

"There has been research into apoptosis [cell death] for decades now. It has long been a goal of the field to see the work translated into actual improved care of cancer patients. AML is a disease in which new therapies are desperately needed, and based on published preclinical work, this type of cancer seemed to be an excellent target for the BCL-2 inhibitor venetoclax," said Anthony Letai, MD, PhD, associate professor of medicine at Harvard Medical School and Dana-Farber Cancer Institute, in Boston, Massachusetts.

Venetoclax is a small molecule that belongs to a class of drugs called BH3 mimetics. It binds with great affinity and selectivity to BCL-2, an antiapoptotic protein that plays a role in many blood cancers, Letai said. BCL-2 proteins keep the AML cells alive by binding to proapoptotic proteins. Venetoclax binds to BCL-2 and frees the proapoptotic proteins, thus rapidly and irreversibly forcing the AML cell to undergo apoptosis, he explained.

In April 2016, venetoclax was [approved](#) by the U.S. Food and Drug Administration for the treatment of certain patients with chronic

lymphocytic leukemia (CLL).

"In this clinical trial, we found that even among pretreated patients whose AML was refractory to intensive chemotherapy, there was evidence of exceptional sensitivity to selective BCL-2 inhibition, even to the point of complete remissions. This could be accomplished by a single oral dose of venetoclax daily and demonstrated the potential clinical activity of BCL-2 inhibition in AML," Letai said.

The study investigators recruited 32 patients with AML with a median age of 71 years to this multicenter, single-arm trial evaluating 800 mg daily oral venetoclax. Twenty-six patients received at least four weeks of therapy.

The overall response rate was 19 percent; two patients had complete response (CR) and four had complete response with incomplete blood count recovery (CRi). The median duration of therapy in responders was 144.5 days, and the median duration of CR was 48 days. All patients discontinued therapy due to progressive disease or an adverse event, or for other reasons.

The investigators performed cytogenetic analysis, BH3 profiling, and next-generation sequencing to look for AML-related genetic mutations in the patients' samples collected at study entry and found that 12 patients had mutations in IDH genes, and six had a high BCL-2-sensitive protein index.

The four patients who had CRi had IDH mutations in their cancer cells. Response to the drug correlated with biomarker results, including indices of BCL-2 protein expression and BH3 profiling, Letai said. "This is significant as it supports the mechanism of action of venetoclax as an on-target inhibitor of BCL-2. Moreover, it offers the possibility of using BH3 profiling as a potential predictive biomarker for clinical use of BH3

mimetics," he added.

Adverse events were as expected and included nausea, diarrhea and vomiting, febrile neutropenia, and hypokalemia.

Lead author of this study, Marina Konopleva, MD, PhD, professor in the Department of Leukemia and the Department of Stem Cell Transplantation at The University of Texas MD Anderson Cancer Center in Houston, said, "We believe that venetoclax will soon become an equal partner to standard-of-care chemotherapy in elderly patients with AML when used in combinations with hypomethylating agents and other approaches. Planned studies will test the hypothesis that venetoclax may likewise improve outcomes in younger AML patients when combined with high-dose chemotherapy."

Letai said, "It is also worth noting that in this age of precision medicine, dominated by genomics, this is an example of the importance of functional precision medicine. CLL and AML lack genetic abnormalities related to BCL-2. Instead, their vulnerability to BCL-2 inhibition was identified using functional studies. This is support that functional studies need to be part of any mature [precision medicine](#) project."

As limitations to the study, most [patients](#) did not meet the criteria of a clinical response, and in those who did respond, the response was not as durable as expected, Letai said. Further, the predictive biomarker assays were performed retrospectively. Subsequent studies will need to perform biomarker studies while blinded to clinical data, he added.

"Marina and I both identified evidence that AML would be a good target for BCL-2 inhibition some years ago. When we realized that we were working on the same idea, we made the conscious decision to collaborate rather than compete," Letai noted. "Combining our work made progress more rapid, and provided more material to convince AbbVie to initiate a

program of venetoclax in AML."

This study was funded by AbbVie in collaboration with Genentech/Roche. Letai has been an advisor to, and his laboratory has received research funds from, AbbVie, AstraZeneca, Tetralogic, and XrX. Konopleva has been a consultant to, and received research funding from, AbbVie, Genentech, Stemline, Eli Lilly and Company, Bristol-Myers Squibb, Calithera, and Cellectis; she is also a stockholder in Reata Pharmaceuticals.

More information: M. Konopleva et al. Efficacy and Biological Correlates of Response in a Phase II Study of Venetoclax Monotherapy in Patients with Acute Myelogenous Leukemia, *Cancer Discovery* (2016). [DOI: 10.1158/2159-8290.CD-16-0313](https://doi.org/10.1158/2159-8290.CD-16-0313)

Provided by American Association for Cancer Research

Citation: Venetoclax safe, shows promise in patients with acute myelogenous leukemia (2016, August 15) retrieved 26 April 2024 from <https://medicalxpress.com/news/2016-08-venetoclax-safe-patients-acute-myelogenous.html>

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