The therapy of acute myeloid leukemia (AML) has lagged behind remarkable advances made in recent years in understanding leukemia biology and genomics. Conventional chemotherapy still remains the mainstay of treatment, and the majority of cases require an allogeneic hematopoietic cell transplant (HCT) for cure. The results of AML therapy are particularly dismal for older patients who are not candidates for intensive therapies as well as for relapsed/refractory cases. Very few of these patients survive beyond 2 years (1).

Relapse or treatment refractoriness in AML can be attributed to small numbers of quiescent leukemia stem cells (LSCs) that are resistant to conventional cytotoxic chemotherapy (2). The lack of progress in AML therapy can largely be attributed to our inability to target LSCs with conventional chemotherapy as well as the poor tolerability of many patients with AML to such therapy. Specifically targeting LSCs therefore remains the holy grail of acute leukemia therapy. A major finding in recent years has been the identification of high levels of BCL2 as a defining characteristic of LSCs (3). Low levels of reactive oxygen species (ROS) have been shown to be a metabolic feature of LSCs, and such ROS-negative LSCs have been shown to aberrantly overexpress BCL2. Moreover, BCL2 inhibition targeted mitochondrial energy metabolism and selectively induced cell death in the LSC compartment (3). The development of the potent BCL2 inhibitors may therefore provide an opportunity to specifically target this quiescent LSC population.

Venetoclax (ABT-199), a BH3 mimetic, is an orally bioavailable, specific inhibitor of BCL2 that is currently approved by the FDA for treatment of chronic lymphocytic leukemia (CLL). Venetoclax binds to BCL2, thereby dislodging proapoptotic proteins like BAK and BAX from their binding to BCL2 (4). Resistance to venetoclax can be mediated by antiapoptotic proteins like BCL-XL and MCL1. Venetoclax has shown potent antileukemic activity in AML cell lines and primary patient samples as well as xenograft models and is currently being tested in clinical trials for AML; see references in ref. 5.

It in this issue, Konopleva and colleagues report the results of a phase II trial of venetoclax monotherapy for patients with AML who had refractory or relapsed disease or were unfit for intensive chemotherapy (5). Of the 32 patients reported, only 26 had at least 4 weeks of therapy, which may have lowered the observed response rate to some extent. Nevertheless, venetoclax monotherapy induced complete morphologic responses (CR; defined as < 5% leukemic blasts) in the bone marrow (CR + CR with incomplete blood count recovery) in 6 patients. Although this constitutes only 19% of treated patients, such results have not been observed with any other oral monotherapy for AML. These results are particularly impressive considering the fact that their cohort consisted of older patients and included many patients with high-risk features including multiple prior therapies and antecedent hematologic disorders as well as adverse cytogenetic and molecular features.

A higher proportion of CR was observed among patients carrying IDH1 or IDH2 mutations. An increased sensitivity of IDH mutants to BCL2 inhibition has been observed in in vitro studies of AML blasts as well (6, 7). This has been attributed to inhibition of cytochrome c oxidase in the mitochondrial electron transport chain by the oncometabolite 2-hydroxymethylglutarate generated by IDH mutations (6). However, other types of AML including those carrying MLL fusions and acute promyelocytic leukemia have shown sensitivity to venetoclax in vitro, and therefore a variety of AML genotypes may be sensitive to venetoclax (8).

The authors have attempted to identify biomarkers of response to venetoclax in leukemic blasts including the ratio of BCL2 to BCL-XL as well as BH3 profiling. Using a series of BH3 peptides to determine interactions between the antia apoptotic BCL2 family proteins and their proapoptotic counterparts, they show a negative correlation between AML blast dependence on the antia apoptotic proteins BCL-XL and MCL1 and duration on venetoclax therapy, suggesting that

**Summary:** Venetoclax is an oral drug with an excellent side-effect profile that has the potential to revolutionize acute myeloid leukemia (AML) therapy in two areas. Venetoclax-based combination therapies could be a bridge to hematopoietic cell transplant with curative intent for patients with refractory/relapsed AML, and venetoclax-based therapy could provide meaningful survival prolongation for older patients with AML who are not candidates for more aggressive therapies. Cancer Discov; 6(10); 1082-3. ©2016 AACR.
the latter proteins are mediators of resistance to venetoclax. In another in vitro study using AML cell lines and primary cells, the IC_{50} of venetoclax was inversely correlated with BCL2/MCL1 transcript ratio, and overexpression of BCL-XL or MCL1 conferred resistance to venetoclax-induced apoptosis in an AML cell line (8). Recently, high expression of HOXA and HOXB genes has been shown to correlate with sensitivity of AML cells to venetoclax (7).

Given the small size of the study reported here by Konopleva and colleagues, their findings of a higher response rate in IDH-mutant AML as well as association of response with biomarkers that determine sensitivity to BCL2 inhibition will have to be confirmed in much larger cohorts of patients with AML. It is also possible that the BH3 profile may differ between peripheral blood or bone marrow blasts and the small population of true LSCs that reside in the bone marrow niche.

Despite their initial response, eventually all patients treated with venetoclax relapsed, and the median time to progression was only 2.5 months. Therefore, resistance seems to develop rather quickly with venetoclax monotherapy. Hence, it appears that in the case of AML, venetoclax is best used in combination with another agent. This is supported by early preclinical and clinical trial data suggesting that venetoclax is at least additive and probably synergistic with a variety of chemotherapeutic agents across various molecular subtypes of AML. Particularly impressive are the preliminary results of an ongoing phase I clinical trial where it has been combined with the hypomethylating agents decitabine or 5-azacytidine (9). This combination achieved an overall response rate of over 70% in a cohort of older patients with AML who were not eligible for standard chemotherapy. No relapse occurred in responders. Another study combining venetoclax with low-dose cytarabine done in a similar high-risk patient population achieved an overall response rate of 44% (10). The side effect profile of venetoclax is excellent, with febrile neutropenia being the most common adverse event. Unlike in CLL, tumor lysis syndrome has not been observed in AML. This makes it possible to administer venetoclax-containing therapy in an outpatient setting in most patients.

In venetoclax, we may finally have an oral drug with an excellent side-effect profile that has the potential to revolutionize AML therapy. Venetoclax-based combination therapies could allow more patients with refractory/relapsed AML to achieve complete remission and undergo allogeneic HCT with curative intent. Venetoclax-based therapy could also provide meaningful survival prolongation for older patients with AML while preserving their quality of life. It appears that by BCL2 inhibition, we may have exploited a key vulnerability of the acute myeloid LSC and translated this into clinical benefit.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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BCL2 Inhibition by Venetoclax: Targeting the Achilles' Heel of the Acute Myeloid Leukemia Stem Cell?

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