Improving Response to FLT3 Inhibitors–BCL2 the Rescue?
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As single agents, FLT3 inhibitors are active in FLT3-mutated acute myeloid leukemia (AML) therapy but not curative. The BCL2 inhibitor, venetoclax, enhances responses to low intensity AML chemotherapy but its activity is limited by MCL1 upregulation. FLT3 inhibitors downregulate MCL1 and synergize with venetoclax in preclinical AML models.

See related article by Ma et al., p. 6815
Figure 1.
A, Venetoclax acts by binding to the hydrophobic groove in the BCL2 protein, displacing proapoptotic activators such as BIM, which interact with BAX and BAK, promoting their insertion into the outer mitochondrial membrane to release cytochrome C and initiate the intrinsic pathway of apoptosis. This effect is antagonized by overexpression of other antiapoptotic proteins such as MCL-1, which bind free BIM and reduce their ability to interact with BAX and BAK. FLT3-ITD mutations promote antiapoptosis in part by overexpression of MCL-1 and stabilization of its expression through activation of MAPK signaling through ERK.

B, FLT3 inhibitors, like midostaurin or gilteritinib, promote apoptosis in part through decrease expression of MCL1, while simultaneously inhibiting ERK phosphorylation, further destabilizing the protein. In combination with venetoclax, FLT3 inhibitors thus facilitate release of proapoptotic BH3-only proteins such as BIM to interact with BAX and BAK to activate apoptosis.
setting, the response rates and survivals observed with low-intensity venetoclax combinations are unprecedented and approach results seen in trials of intensive regimens in fit patients. Importantly, venetoclax achieved these results with relatively modest and manageable side effects, and in vitro screens of venetoclax combinations suggest drugs from a number of novel mechanistic classes might exert clinical synergy with this agent (3).

Following approval, use of venetoclax in AML has become widespread. Therefore, it is important to develop strategies to circumvent venetoclax resistance mechanisms in designing combination regimens. Overexpression of other antiapoptotic proteins, primarily MCL-1, has also been implicated in venetoclax resistance and, because the stability of MCL-1 protein is regulated by ras/MAPK signaling, this pathway’s activation potentially also contributes to BCL2 inhibitor resistance (Fig. 1; refs. 4, 5). Accordingly, clinical trials of MCL-1 inhibitors and MAPK pathway inhibitors, alone or in combination with venetoclax, have been initiated. But neither of these drug classes have validated clinical efficacy in AML and, mechanistically, FLT3 mutations are among the most common mechanisms for MAPK pathway activation in AML. This suggests FLT3 and BCL2 inhibitors may have complementary roles to maximize efficacy while avoiding resistance.

Ma and colleagues show that the FDA-approved FLT3 inhibitors, midostaurin and gilteritinib, downregulate MCL-1 expression in FLT3-mutated AML cell lines and primary samples and acutely inhibit ERK phosphorylation, resulting in synergistic antileukemic cytotoxicity when combined with venetoclax. It is notable that single agent FLT3 inhibitor or venetoclax treatment in vitro shows limited apoptosis in either FLT3-mutated cell lines or primary patient samples. However, the combination of either FLT3 inhibitor with venetoclax strongly induced apoptosis as measured by cleaved caspase 3 and/or annexin V/PI positivity. In addition, a murine xenograft model of FLT3-mutated AML showed prolonged survival to the combination of venetoclax and gilteritinib, with essentially all mice succumbing to single-agent therapy with either agent administered alone for 4 weeks and only a modest observed survival advantage with single agent gilteritinib over vehicle. This is not the first publication to demonstrate synergy between FLT3 and BCL2 inhibitors, but it is noteworthy for combining highly selective inhibitors of each target, and provides greater assurance that the observed mechanism underlying synergy is sound.

The authors also make some interesting observation that require further mechanistic analysis, including the unexpected finding of ERK activation with prolonged in vitro incubations of single agent FLT3 inhibitors, along with in vitro cytotoxicity of gilteritinib in numerous patients lacking FLT3 mutations. These observations may point to new avenues to further enhance response or they may merely relate to the specific cells, culture conditions, and/or relatively high inhibitor concentrations studied. At present, it is probably premature to extrapolate these findings beyond the intended clinical application of FLT3-mutated patients.

Although novel drugs are often approved as single agents, the genetic and biologic complexity of AML encourages exploration of rational novel therapeutic combinations to maximize efficacy. Ma and colleagues may have hit upon an important interaction between two important classes of new agents. These preclinical data are exciting and hint that ongoing trials examining combinations of FLT3 inhibitors and venetoclax may indeed bear fruit (NCT03625505 and NCT03735875).

Disclosure of Potential Conflicts of Interest
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