New Combination Therapy Offers Potential to Cure *FLT3*-ITD Acute Myelogenous Leukemia

By Roberto Molar-Candanosa

A new combination therapy using plerixafor, granulocyte colony-stimulating factor (G-CSF), and sorafenib may lead to lasting remissions—and possibly even a cure—for patients with acute myelogenous leukemia (AML) carrying the internal tandem duplication (ITD) mutation in the Fms-like tyrosine kinase 3 (*FLT3*) gene.

The leukemic cells of about 30% of AML patients harbor the *FLT3*-ITD mutation, making it one of the most frequent mutations of AML. With standard AML therapy, these patients have a median survival of only 9 months, and less than 5% are cured.

Several inhibitors of the FLT3 kinase, including the multiple kinase inhibitor sorafenib, have shown activity against *FLT3*-ITD AML, but none has produced lasting responses in single-agent clinical trials. The new combination therapy is designed to overcome the mechanisms responsible for drug resistance.

Resistance to FLT3 inhibition

One reason for the lack of durable response to *FLT3*-ITD AML treatment with single-agent FLT3 inhibitors is the protective effect of stromal cells in the bone marrow. *FLT3*-ITD mutations activate signaling of the chemokine receptor CXCR4 and its ligand, stromal-derived factor 1 (SDF-1), in the bone marrow. Once activated, the SDF-1/CXCR4 signaling pathway regulates leukemic cell proliferation and mobilization, resulting in resistance to therapy.

In preclinical studies, the combination of the CXCR4 inhibitor plerixafor and G-CSF was able to mobilize leukemic cells out of the bone marrow's protective microenvironment and into the bloodstream, where the leukemic cells could be killed by sorafenib. Preclinical studies also showed that plerixafor and G-CSF selectively mobilize leukemic blasts and stem cells and inactivate CXCR4 and other adhesion molecules that bind leukemic cells to the bone marrow. In addition, these studies revealed a mechanism by which CXCR4 inhibition directly sensitizes leukemic cells to chemotherapy via a complex network of transcription factors, microRNAs, and cell death regulators.

Clinical trial

The new combination therapy was tested at The University of Texas MD Anderson Cancer Center in a phase I clinical trial that opened in 2010 and recently completed enrollment. The clinical trial was the first to use plerixafor, G-CSF, and sorafenib to mobilize and kill leukemic cells.

Eligible patients were 18 years or older and had relapsed or refractory *FLT3*-ITD AML. The patients received injections of plerixafor (240 mg/kg) and G-CSF (10 mg/kg) every other day on days 1–13 and oral sorafenib (400–600 mg) twice daily in 28-day cycles.

The overall response rate for patients in the study was 64%: 36% had complete remissions, and another 28% had partial remissions. There were no treatment-related deaths. Also, the combination therapy was shown to be safe for normal stem cells.

Michael Andreeff, M.D., Ph.D., a professor in the Department of Leukemia and the principal investigator of the study, presented the results in June at the 2014 American Society of Clinical Oncology Annual Meeting. "In addition to the high response rates, what was particularly interesting is that we had two patients in the trial who previously had unsuccessful bone marrow transplants but with the new combination therapy had complete remissions lasting 1 year and almost 2 years," Dr. Andreeff said. "With more effective agents that are now becoming available, this therapeutic strategy offers the potential of curing *FLT3*-ITD AML." ■

FOR MORE INFORMATION

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