Ficlatuzumab plus chemotherapy may benefit patients with relapsed/refractory AML

16 July 2021

The investigational therapeutic ficlatuzumab in combination with chemotherapy showed signs of clinical efficacy in patients with relapsed/refractory acute myeloid leukemia, according to results published in *Blood Cancer Discovery*, a journal of the American Association for Cancer Research.

"Only about half of patients with acute myeloid leukemia (AML) will achieve long-term disease control," said Charalambos Andreadis, MD, professor of clinical medicine at the University of California, San Francisco (UCSF) and senior author of the study. Patients whose AML relapses or does not respond to initial therapy have worse outcomes, Andreadis explained. These patients typically undergo subsequent multi-agent chemotherapy, a toxic treatment with limited success in this population, he added.

"Unfortunately, patients whose cancers relapse or don't respond to initial therapy face a poor outlook, as only 30 to 40 percent of these patients respond to subsequent multi-agent chemotherapy and even fewer develop long-term remissions. Most patients will eventually succumb to their disease," he said.

New therapies targeting AML-specific mutations have been developed in recent years; however, these target select patients, highlighting the need for new, widely applicable therapies, according to Andreadis.

In their study, Andreadis and colleagues evaluated the safety and efficacy of an investigational agent targeting a shared chemical pathway in combination with single-agent chemotherapy in patients with relapsed/refractory AML. The investigational therapy, ficlatuzumab, is a first-in-class monoclonal antibody that binds the extracellular hepatocyte growth factor (HGF) to prevent it from activating MET signaling and stimulating tumor growth. "Unlike most existing targeted cancer therapies, ficlatuzumab targets an extracellular factor instead of a cancer-specific mutation," Andreadis noted, adding that some patients with refractory AML have higher levels of circulating HGF.

The phase I clinical trial enrolled 17 adult patients with AML that was either refractory to prior treatment or that had relapsed within 12 months of prior treatment. Patients received four doses of ficlatuzumab, administered 14 days apart, along with the chemotherapeutic cytarabine.

Nine of 17 patients (53 percent) had a complete response, and four of the responding patients had no signs of minimal residual disease. Among responding patients, the progression-free survival was 31.2 months, and the overall survival was not reached. Ten patients (eight responders and two non-responders) proceeded to allogeneic hematopoietic cell transplantation; six of these patients remained in remission at the most recent follow-up.

The most common adverse event was febrile neutropenia. Serious adverse events occurred in two patients, and there was one death unrelated to the investigational therapy.

"The 53 percent response rate was quite striking to us since historical response rates for the standard-of-care treatment are in the 30 percent range," noted Andreadis. "While these results need to be validated in a larger study, they suggest that ficlatuzumab in combination with single-agent chemotherapy may lead to better responses with less toxicity in patients with relapsed/refractory AML."

To identify molecular changes associated with

treatment response, Andreadis and colleagues analyzed peripheral blood mononuclear cells collected at baseline and at several timepoints after treatment initiation. They found that ficlatuzumab treatment led to attenuated phosphorylation of MET, the receptor for HGF, thereby confirming on-target inhibition of HGF. Clinical response to ficlatuzumab treatment was associated with reduced phosphorylation of the S6 protein and increased expression of genes involved in myeloid and leukocyte activation, whereas non-responding patients were more likely to have increased expression of HGF, increased phosphorylation of S6, and expression of genes involved in protein translation, cell adhesion, and type I interferon signaling.

"By comparing pre-treatment to post-treatment blood samples using state-of-the art single-cell mass cytometry and RNA sequencing, we observed that ficlatuzumab successfully suppressed HGF signaling, and we also identified biomarkers of treatment response and resistance," said the study's first author, Victoria Wang, MD, Ph.D., an assistant professor of hematology and oncology at UCSF. "This approach provided novel insight into the molecular changes that occur upon treatment, which could have clinical implications for tracking treatment response or identifying patients likely to respond."

"Together, our findings suggest that targeting an extracellular factor in conjunction with existing cancer therapies could be an effective therapeutic strategy for AML treatment," said Andreadis.

Limitations of the study include the small sample size and its single-arm design. Andreadis and Wang noted that since the study was designed to assess safety and dosing, rather than efficacy, additional studies to validate the efficacy findings will be needed. A phase II clinical trial to evaluate ficlatuzumab plus chemotherapy has been initiated. An additional limitation was the lack of bone marrow specimens for the gene expression analyses.

More information: Inhibition of MET Signaling with Ficlatuzumab in Combination with Chemotherapy in Refractory AML: Clinical Outcomes and High-Dimensional Analysis, *Blood Cancer Discovery*, DOI: 10.1158/2643-3230.BCD-21-0055 , bloodcancerdiscov.aacrjournals ... 643-3230.BCD-21-0055

Provided by American Association for Cancer Research