Novel menin inhibitors show promise for patients with advanced acute myeloid leukemias

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Two clinical trials led by researchers from The University of Texas MD Anderson Cancer Center demonstrated early positive results from novel therapies targeting menin for the treatment of relapsed or refractory acute leukemias with specific genetic alterations.

Results from the studies were shared in oral presentations at the 2023 American Society of Hematology (ASH) Annual Meeting.

Menin inhibitor monotherapy reduces disease burden in majority of relapsed or refractory acute leukemia patients

According to data from a Phase I trial led by Elias Jabbour, M.D., professor of Leukemia, the menin inhibitor JNJ-75276617 showed early clinical activity in patients with relapsed or refractory acute leukemias and genetic alterations in KMT2A or NPM1, which are associated with poor clinical outcomes.

Among 66 patients able to be evaluated after one month of treatment, JNJ-75276617 monotherapy reduced bone marrow disease burden in 71%, and 33 of those patients had a decrease in bone marrow blasts of more than 50%. Median time to first response was less than two months. Similar response rates were observed across patient groups with both genetic alterations.

"Patients with relapsed or refractory leukemias and KMT2A or NPM1 alterations often do poorly on currently available therapies, so there is a need to advance more effective options," Jabbour said. "We are encouraged by the antileukemic activity of this monotherapy, which mimics what we saw in the preclinical setting."

In the multi-center clinical trial, researchers took a stepwise approach in evaluating the safety and efficacy of JNJ-75276617, a potent and selective inhibitor of the interaction between the scaffolding protein menin and the methyltransferase KMT2A. Eighty-six patients who had acute leukemias with NPM1 & KTM2A genetic alterations were included in the trial.

Patients received the therapy orally on a 28-day cycle. Fifty-six percent of evaluable patients had AML with KMT2A alterations and 43% of evaluable patients had NPM1 alterations. The median age of trial participants was 63 years, while the median number of prior therapies was two.

Differentiation syndrome was the most common side effect in patients, but was overcome with step-up dosing. The trial is ongoing to determine the recommended Phase II dose.

Oral therapy combination shows promising results for advanced acute leukemias

The Phase I/II SAVE trial, led by Ghayas Issa, M.D., assistant professor of Leukemia, combined the menin inhibitor revumenib with venetoclax and hypomethylating agent ASTX727, yielding encouraging responses in adult and pediatric patients with relapsed or refractory advanced acute myeloid leukemia (AML) with KMT2A or NUP98 rearrangements or NPM1 mutations.

The overall response rate among nine evaluable patients was 100%. Three patients achieved complete remission, one patient achieved complete remission with partial hematologic recovery, and three patients had complete remission with incomplete platelet count recovery. In addition, one patient had a partial response and one had a morphologic leukemia-free state. Measurable residual disease was undetectable in six of the patients.

"These advanced and acute leukemias often are very difficult to treat and currently have no approved targeted therapies. We believe these early results suggest this treatment will be highly effective in advanced leukemias," Issa said. "This is our first look at an entirely oral

combination therapy using menin inhibitors, and the results are very encouraging. If sustained in further trials, this could lead to a change in the standard of care for this patient population, with great potential to improve their quality of life."

Revumenib is a potent, oral, selective inhibitor of the menin-KMT2A interaction. To date, nine patients aged 12 years and older have been enrolled in the trial. Of those, five patients had KMT2A rearrangements, three had NUP98 rearrangements and one had mutant NPM1. On average, patients had received three prior lines of therapy.

Side effects were manageable and consistent with previous studies. The trial is ongoing, with plans to establish the recommended Phase II dose and optimize delivery of the combination before enrolling patients in the Phase II cohort.

More information:

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Provided by University of Texas M. D. Anderson Cancer Center