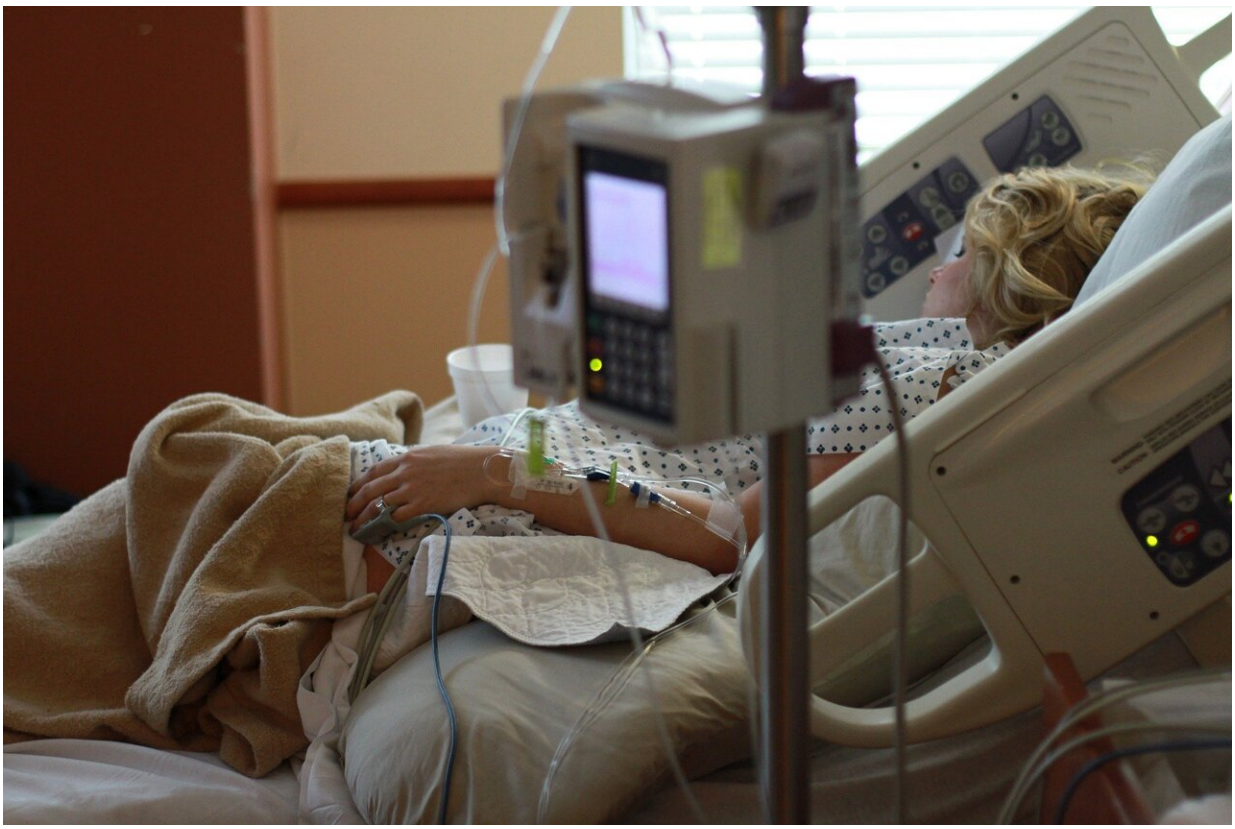
Medical Xpress

Combination therapy well-tolerated and highly effective for patients with IDH1-mutated AML

May 28 2020



Credit: CC0 Public Domain

A combination therapy of ivosenidib (IVO) plus venetoclax (VEN) with or without azacitidine (AZA) was found to be effective against a specific

genetic subtype of acute myeloid leukemia (AML) in a Phase Ib/II trial led by researchers at The University of Texas MD Anderson Cancer Center. The results of this trial may support a novel course of action for patients with AML harboring an IDH1 mutation who have historically had few treatment options.

Across all treatment groups, the composite complete remission rate was 78% overall and 100% for treatment-naïve patients. Half of the patients who achieved complete remission also were negative for minimal residual disease (MRD). The results were presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting by lead author Curtis Lachowiez, M.D., hematology fellow.

"This trial is the manifestation of remarkable basic and translational work that is resulting in improved clinical outcomes for patients," said Lachowiez. "The triplet combination may ultimately result in a new, effective therapeutic regimen. As the median age at AML diagnosis is 68, these findings are particularly important for older AML patients who may not be fit enough to receive the aggressive cytotoxic chemotherapy regimens historically used to treat AML."

Mutations in the IDH1 gene lead to myeloid differentiation arrest and subsequent induction of leukemia. IVO, as an IDH1 inhibitor, is a well-tolerated oral therapy that aims to interrupt this leukemogenic process.

The combination of VEN and AZA was previously established to be well-tolerated and effective against newly diagnosed AML, and IVO is approved as a single agent for relapsed IDH1-mutated AML. This trial sought to evaluate the safety, tolerability, and response rate of adding this targeted therapy, IVO, to either venetoclax alone as an oral doublet, or to the AZA and VEN combination to treat this subset of AML patients with a specific genetic mutation.

"To our knowledge, AZA plus VEN and AZA plus IVO 'doublets' are effective but not curative for newly diagnosed IDH1-mutated AML patients, and patients still ultimately relapse. This triplet combination trial aims to determine whether this regimen leads to deeper responses and even curative therapy in some patients," said Courtney DiNardo, M.D., associate professor of Leukemia and the study's senior author. "Additionally, this trial evaluates the oral IVO plus VEN doublet for the first time, and we hope patients will benefit from this outpatient regimen."

Patients with AML or high-risk myelodysplastic syndrome (MDS) were assigned one of three cohorts, either receiving IVO + VEN 400 mg, IVO + VEN 800mg or IVO + VEN 400mg + AZA.

The median time to best response was two months. Of the 18 evaluable patients, nine remain enrolled in the study, and three proceeded to receive a stem cell transplant following complete remission.

"This study is exciting because it displays that we are able to tailor therapy for AML patients based on their molecular profile," said Lachowiez. "While some mutations have traditionally been associated with poor outcomes, we can now identify certain subgroups of patients with genetic mutations who are more likely to respond to a specific therapy, and then we can design a treatment and follow-up plan to best suit them."

Based on a patient's molecular profile, their care team may be able to decide on options like closer monitoring or earlier transition to transplant for high-risk patients. Further, as in the case of patients with molecular mutations associated with favorable responses, the care team may be able to prescribe tailored therapeutic combinations, leading to durable remissions and potential cures.

Study accrual is continuing, and the research team is conducting additional follow-up to elucidate the biomarkers and potential duration of response.

More information: Curtis Andrew Lachowiez et al. Phase Ib/II study of the IDH1-mutant inhibitor ivosidenib with the BCL2 inhibitor venetoclax +/- azacitidine in IDH1-mutated hematologic malignancies. *2020 American Society of Clinical Oncology (ASCO) Annual Meeting* meetinglibrary.asco.org/record/185312/abstract

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