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General AML

Venetoclax plus azacitidine can target leukemia stem cells and metabolism in acute myeloid leukemia

Cynthia Umukoro | Jan 14, 2019

Overexpression of the B cell lymphoma 2 (BCL-2) protein has been shown to be associated with poor outcomes in patients with acute myeloid leukemia (AML). In addition, the BCL-2 protein is overexpressed in leukemia stem cells (LSCs).

Data from a dual-stage, non-randomized phase Ib dose-escalation and expansion study (NCT02203773) of venetoclax, a BCL-2 inhibitor, in combination with hypomethylating agents demonstrated that this regimen was well-tolerated and induced deep durable responses in elderly patients with newly diagnosed AML. The LSC-directed mechanism of venetoclax plus azacitidine in 33 patients who were treated in this phase I study was investigated by a group of researchers from the University of Colorado School of Medicine. The results of the study were reported in *Nature Medicine*.

In this study, the clinical outcomes of the 33 patients (median age = 75 years; range, 65–89) who were treated with venetoclax and azacitidine, at the University of Colorado School of Medicine as part of the phase Ib study, were first compared to 88 control patients aged > 59 years with newly diagnosed AML who had intermediate to adverse cytogenetics and were consecutively treated with any therapy besides venetoclax plus azacitidine.

Key findings:

Clinical outcomes for the 33 AML patients treated with venetoclax plus azacitidine

- Overall response rate: 91% (30/33)
- Median time to response: 34.5 days (range, 25–62)
- Median follow-up time: 580 days (95% CI, 377–713)
- Median response duration, progression-free survival, and overall survival have not been reached

Comparison of the clinical outcomes of patients treated with venetoclax and azacitidine and control patients who received any other therapy, respectively

- Complete remission (CR)/CR with incomplete count recovery (CRi): 85% *vs* 51% (z-score = −3.102; P = 0.0019)
- Median overall survival: not reached *vs*5 days (P = 0.0003)

Peripheral blood samples from patients with circulating diseases were analyzed to further investigate the cellular events accompanying response to venetoclax and azacitidine

- There were rapid decreases in peripheral blood blasts in patients with circulating disease with a significant reduction within 24 hours and complete eradication within six days following treatment
- There was a significant eradiation of phenotypically defined LSCs ($CD34^+$, $CD38^-$, Lin^-, $CD123^+$)
- RNA-seq analysis of low reactive oxygen species isolated after 6 hours of treatment demonstrated that pathways related to OXPHOS (a pathway critical for LSC maintenance and survival) were strongly downregulated

Metabolomics analyses were performed on pre- and 24 hours post-treatment samples obtained from patients treated with venetoclax and azacitidine

- It was observed that there was a decrease in OXPHOS post-treatment in patients treated with venetoclax and azacitidine which was not detected in patients treated with standard induction chemotherapy
- *In vitro* treatment of LSCs, isolated from patients, for 4 hours with azacitidine demonstrated a reduction in OXPHOS
- Decreased OXPHOS led to a reduction in ATP levels in LSCs treated with azacitidine and venetoclax
- Venetoclax plus azacitidine reduces complex II activity through a reduction in SDHA glutathionylation

In summary, venetoclax plus azacitidine is highly active in older, previously untreated patients with AML; responses are deep and durable, and outcomes are superior compared with historical controls. In addition, therapy with venetoclax and azacitidine can effectively eradicate the LSC compartment via targeting LSC-specific metabolic properties.

The researchers concluded that their findings “show for the first time that therapeutic intervention can eradicate LSCs in patients with AML by disrupting the metabolic machinery driving energy metabolism, resulting in promising clinical activity in a patient population with historically poor outcomes.”

References

1. Pollyea D. A., Stevens B.M., Jones C. L. *et al*. Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. Nat Med. 2018 Nov 12; 24: 1859–1866. DOI: 10.1038/s41591-018-0233-1.