ABT199/Venetoclax synergism with thiotepa in acute myeloid leukemia (AML) cells

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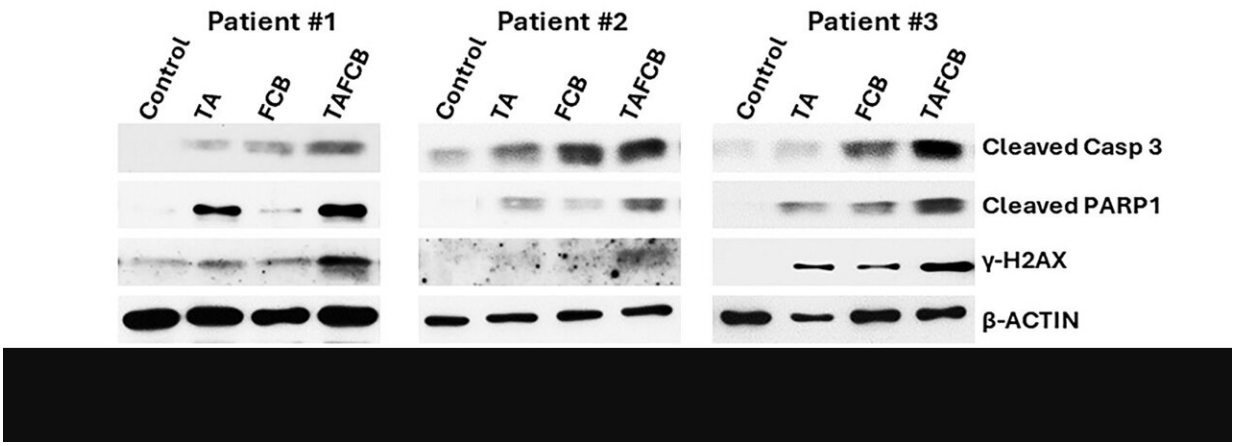
Characteristics of patients whose cell samples were used in the study

Patient	Age, yrs	Gender	Race	Diagnosis	Cytogenetics
1	63	Male	Caucasian (Hispanic)	T-cell prolymphocitic leukemia	46, XY FISH: ALK (-), JAK2 (-), BCR/ABL1 (-)
2	19	Female	Black	Mixed phenotype acute leukemia	45,XX,-9,-15,del(16)(p11.2p12.2),+der(?)t(?;9)(?;q32)[10]/45,idem,add(17)(q25)[10]
3	32	Female	Caucasian	Acute myeloid leukemia	Not Determined



Effects of various drug combinations on molecular markers of apoptosis in patient-derived cell samples. Credit: *Oncotarget* (2024). DOI: 10.18632/oncotarget.28563

A new research paper titled "ABT199/venetoclax synergism with thiotepa enhances the cytotoxicity of fludarabine, cladribine and busulfan in AML cells" has been published in *Oncotarget*.

ABT199/venetoclax, an inhibitor of the pro-survival BCL-2 protein, has improved AML treatment. However, its efficacy in hematopoietic stem cell transplantation (HSCT) when combined with other chemotherapeutic drugs has not been thoroughly investigated. In this new study, researchers Benigno C. Valdez, Bin Yuan, David Murray, Jeremy L. Ramdial, Uday Popat, Yago Nieto, and Borje S. Andersson from The University of Texas MD Anderson Cancer Center and the University of Alberta demonstrate the synergistic cytotoxicity of ABT199/venetoclax with the DNA alkylator thiotepa (Thio) in AML cells.

The researchers posit, "The results may provide relevant information for the design of clinical trials using these drugs to circumvent recognized drug-resistance mechanisms when used as part of pre-transplant conditioning regimens for AML patients undergoing allogenic HSCT."

Cleavage of Caspase 3, PARP1 and HSP90, as well as increased Annexin V positivity, suggests potent activation of apoptosis by this two-drug combination; increased levels of γ-H2AX, P-CHK1 (S317), P-CHK2 (S19) and P-SMC1 (S957) indicate an enhanced DNA damage response. Likewise, the increased level of P-SAPK/JNK (T183/Y185) and decreased P-PI3Kp85 (Y458) suggest enhanced activation of stress signaling pathways. These molecular readouts were synergistically enhanced when ABT199/venetoclax and Thio were combined with fludarabine, cladribine and busulfan.

The five-drug combination decreased the levels of BCL-2, BCL-xL and

MCL-1, suggesting its potential clinical relevance in overcoming ABT199/venetoclax resistance. Moreover, this combination is active against P53-negative and FLT3-ITD-positive cell lines. Enhanced activation of apoptosis was observed in leukemia patient-derived cell samples exposed to the five-drug combination, suggesting a clinical relevance.

"The results provide a rationale for clinical trials using these two- and five-drug combinations as part of a conditioning regimen for AML patients undergoing HSCT," the researchers conclude.

More information: Benigno C. Valdez et al, ABT199/venetoclax synergism with thiotepa enhances the cytotoxicity of fludarabine, cladribine and busulfan in AML cells, *Oncotarget* (2024). DOI: 10.18632/oncotarget.28563

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