Abstract: P380

Title: SYNERGISTIC EFFECT OF CHIDAMIDE AND VENETOCLAX IN IKZF1 DELETION ACUTE B LYMPHOBLASTIC LEUKEMIA CELLS AND ITS MECHANISM

Abstract Type: Poster Presentation

Topic: Acute lymphoblastic leukemia - Biology & translational research

Background:

IKZF1 deletion acute B-cell lymphoblastic leukemia (IKZF1delB-ALL) is an aggressive blood cancer with an adverse outcome. However, there is a lack of effective targeted drugs for IKZF1del, emphasizing the critical need for new or adjunctive therapies that can improve outcomes. Selective Bcl-2 inhibitor venetoclax has been revealed responses in various hematologic malignancies. However, venetoclax resistance often occurs due to up-regulation of alternative anti-apoptotic proteins. We previously reported that HDAC inhibitor chidamide Inhibits proliferation and repressed cell glycometabolism but does not induce apoptosis in IKZF1delB-ALL, indicating limitations as monotherapy.

Aims:

To evaluate whether chidamide combined with venetoclax could produce a synergistic anti-IKZF1delB-ALL effect and determine the underlying mechanisms.

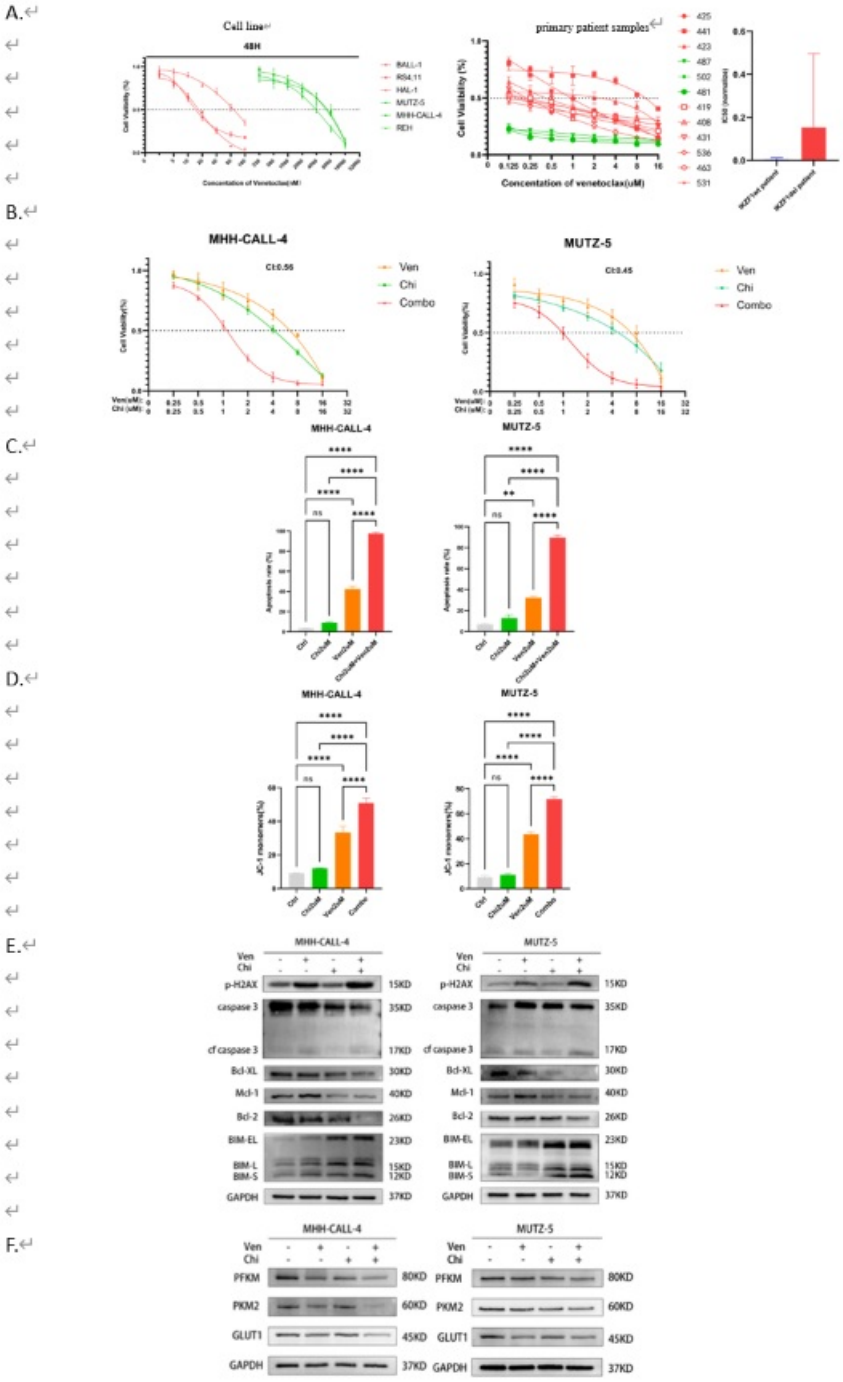
Methods:

The effect of chidamide and venetoclax combination on cell viability, apoptosis, mitochondrial membrane potential (MMP) was investigated in vitro using B-ALL cell lines (IKZF1del: MUTZ-5, MHH-CALL-4, IKZF1wt: RS4;11, HAL-1, BALL-1) and primary patient samples (n=12, 8 with IKZF1del and 4 with IKZF1wt). Western blotting was used to investigate the changes in protein expression within the Bcl-2 family protein and glycometabolism.

Results:

IKZF1delB-ALL cell lines and primary patient samples were resistant to venetoclax compared to IKZF1wtB-ALL(Fig. A). When we combined venetoclax with chidamide, a significant synergistic effect was observed (combination index <1)(Fig. B). Chidamde monotherapy does not significantly induce apoptosis and decrease the MMP in IKZF1delB-ALL cells, but it can greatly increase the pro-apoptotic and decrease MMP effect of venetoclax(Fig. C, D). In two IKZF1delB-ALL cell lines MHH-CALL-4 and MUTZ-5, at the protein levels, the expression of Mcl-1 was upregulated by venetoclax and downregulated by chidamide, and the expression of Mcl-1 decreased further after combination treatment(Fig. E). In addition, the expression of Bcl-2 and Bcl-xl were unchanged by monotherapy but downregulated after combination treatment(Fig. E). In contrast, the combination of chidamide and venetoclax resulted in BIM upregulation and DNA double-strand breaks marker γ-H2AX(Fig. E). As for glycometabolism enzymes, the combination of two drugs resulted in PKM2, PFKM, and GLUT1 downregulated(Fig.F).

Summary/Conclusion: Our study reveals synergy with chidamide and venetoclax combination therapy in IKZF1delB-ALL, warranting pre-clinical trials for patients with IKZF1delB-ALL.(This work was supported by National Natural Science Foundation of China [81970147, 82170163]Clinical Trial Funding of Nanfang Hospital, Southern Medical University [2023CR009], BeijingXisike Clinical Oncology Research Foundation [CHIPSCREEN (to HZ), JW Therapeutics (to HZ)]).



Keywords: BCL2, HDAC, Ikaros, Acute lymphoblastic leukemia