Dual Targeting of FLT3 Signaling and BCL2 Dependency by Venetoclax in ATO-Resistant FLT3-ITD Acute Promyelocytic Leukemia

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INTRODUCTION

Arsenic trioxide (ATO) virtually cures all the patients of Acute Promyelocytic Leukemia (APL). However, acquired resistance to ATO has been reported in APL. However, FLT3-ITD mutations, found in 20-30% of high-risk cases and enriched in the bcr3 isoform, confer hyperleukocytosis, early mortality, and inferior outcomes.

AIM

To evaluate the efficacy of venetoclax in overcoming ATO-resistant-FLT3-ITD+APL.

METHOD

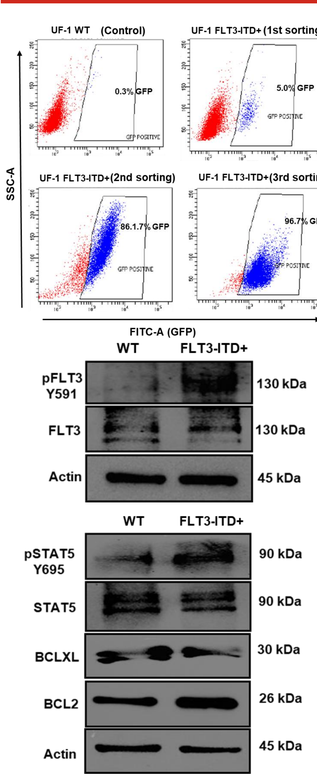
- The intrinsically ATRA/ATO-resistant, bcr3-isoform UF-1 APL cells, were stably transduced with an FLT3-ITD-MSCV-IRES-GFP lentiviral construct to generate an ectopically expressing FLT3-ITD+APL model, confirmed by phospho-FLT3 (Y591) immunoblotting.
- Downstream signaling (pSTAT5, BCL2, BCL-XL) was assessed by immunoblots.
- IC_{50} values for midostaurin and venetoclax were determined, and their effects on FLT3 downstream signaling were evaluated.
- Therapeutic efficacy was further validated in an orthotopic NOD/SCID xenograft model, with leukemic burden quantified by $hCD45^{+}$ flow cytometry and spleen weight measurement.

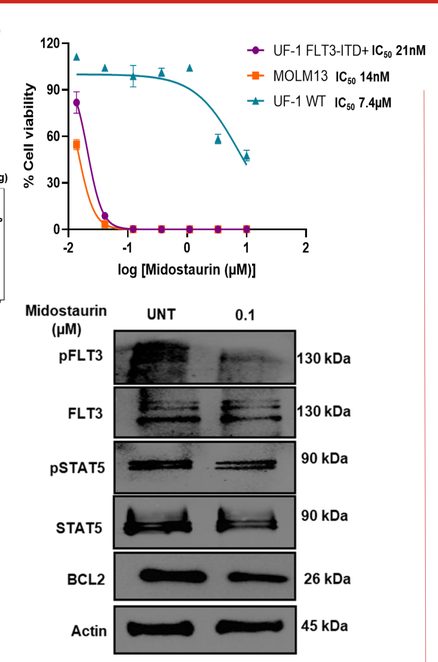
CONCLUSIONS

Beyond direct BCL2 inhibition, venetoclax suppresses the constitutive FLT3/STAT5 signaling axis, providing mechanistic insight into its anti-leukemic activity in FLT3-ITD+APL.

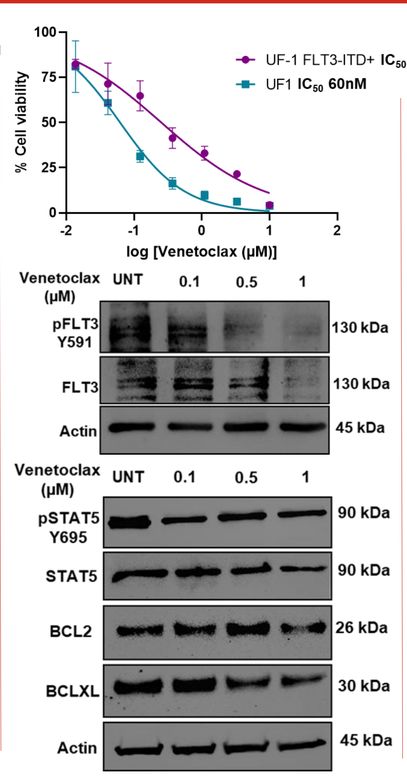
These findings establish venetoclax-based therapy as a rational preclinical strategy for ATO-resistant FLT3-ITD+APL and support its further clinical evaluation.

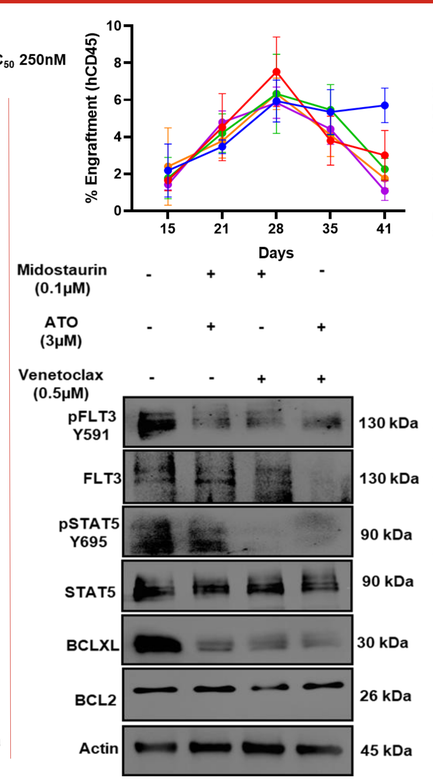
RESULTS

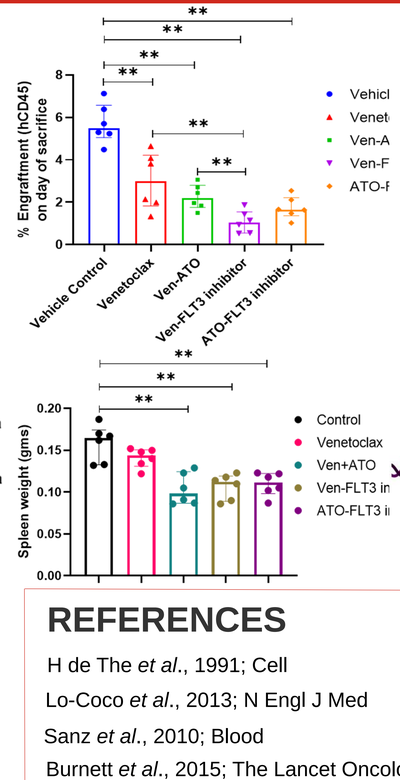


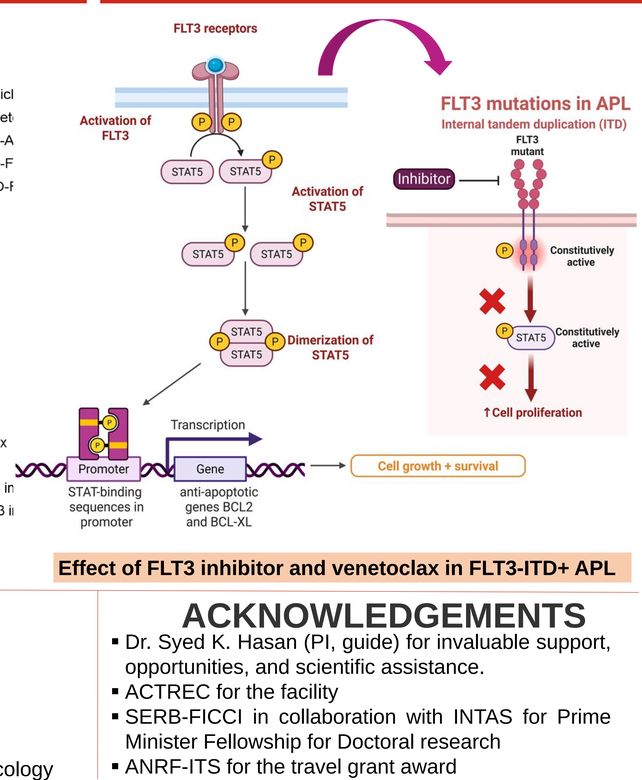


Enhanced FLT3 signaling downstream cascade in FLT3-ITD+ APL cells inhibited by FLT3 inhibitor









Effect of FLT3 inhibitor and venetoclax in FLT3-ITD+ APL

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