THE CLINICAL MENIN INHIBITOR ZIF TOMENIB AND THE NUCLEAR EXPORT INHIBITOR SELINEXOR SYNERGISTICALLY INHIBIT THE GROWTH OF MLL-R AML

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INTRODUCTION

Menin is a scaffold protein that interacts with oncogenic histone-lysine-N-methyltransferase MLL (KMT2A)-fusion protein (PP) complex in MLL-rearranged (MLL-R) AML. Menin inhibitors that exist menin from this interaction have been shown to be active against MLL-R and NPM1MT leukemia by modulating the expression of the leukemic transcription factor ASH (HOXA9) gene and its co-factor, MEIS1 (top and bottom panel).

Recent evidence showed that menin inhibitors can activate a tumor-suppressive network via a non-canonical transcriptions program through UTX (bottom panel).

On the other hand, selective inhibitor of nuclear export (SINE) against XPDTM-1 (MEN1) has been shown to have robust anti-leukemia activity via enrichment of tumor suppressor proteins in the nucleus (right panel).

In the present study, we hypothesized that menin and nuclear export inhibition would synergistically suppress AML cell proliferation and possibly sensitize menin inhibitor-resistant cells.

We have used the clinical-stage menin inhibitor zifotomenib and SINE compound selinexor to simultaneously target menin (KMT2A) protein-protein interactions and nuclear export.

METHODS

- An ATP-based cell proliferation assay was used to assess growth inhibition.
- Combination synergy was determined using CalcuSyn Version 2.0 synergy software.
- Stem-line progenitor cells were isolated using the StemSpan CD34+ expansion kit (StemCell Tech).
- Colony formation efficiency was determined using a Methocult assay (StemCell Tech).
- Gene and protein expression and cell death were detected using quantitative real-time PCR, western-blotting.
- Flow cytometric analysis was performed to detect cell death and cell cycle status.
- We performed whole transcriptomic analysis via RNA sequencing approach and global proteomic analysis.

RESULTS

- The clinical candidate zifotomenib, in combination with selinexor, synergistically inhibited the growth of MLL-R AML cells (MV4-11, MOLM-3, and SEMI-CI < 1).
- The combination affected cell cycle pathway via the downregulation of multiple proteins, including CDK4.
- These preclinical findings demonstrate that simultaneous inhibition of the menin-KMT2A interaction and nuclear export is a viable strategy for treating MLL-R AML.
- Further studies on menin inhibitor resistance cells and other xenograft studies are ongoing.

REFERENCES


CONCLUSIONS

- The clinical candidate zifotomenib, in combination with selinexor, synergistically inhibited the growth of MLL-R AML cells (MV4-11, MOLM-3, and SEMI-CI < 1).
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ACKNOWLEDGEMENTS

Funding source: 1. Kura Oncology
2. SP30CA224453-41 [CCSG KCI]
Figure (8A,B,8I) were created with BioRender.com