(PS1536) TARGETING MCL-1 WITH CARDIO-SAFE DEGRADER CT-03P EXERTS ACTIVITY IN AML AND OVERCOMES VENETOCLAX RESISTANCE

Topic: 03. Acute myeloid leukemia - Biology & translational research

Mak Po Yee[1], Pawel Dobrzanski[2], Abhishek Maiti[3], Tomasz Tomczyk[2], Sylvain Cottens[2], Michal Walczak[2], Michael Andreeff[1], Bing Carter*[1]

[1]The University of Texas MD Anderson Cancer Center, Section of Molecular Hematology and Therapy, Department of Leukemia, Houston, United States of America; [2]Captor Therapeutics, Wroclaw, Poland; [3]The University of Texas MD Anderson Cancer Center, Department of Leukemia, Houston, United States of America;

Background

BCL-2 inhibitor venetoclax/hypomethylating agent regimen are highly effective in inducing remissions in AML. However, majority of patients relapse due to the activation of oncogenic signaling pathways that stabilize MCL-1, a key resistance factor to venetoclax, or through TP53 mutation-mediated downregulation of pro-apoptotic proteins. We reported that MCL-1 not only directly protects leukemia cells from apoptosis but also exerts other functions that support leukemia growth and survival including regulating metabolic activities (Carter et al., Haematologica 2022). Several MCL-1 inhibitors have been developed and entered clinical trials in AML. However, increased troponin levels, suggesting potential cardiotoxicity in patients treated with MCL-1 inhibitors curbed their clinical development. Unlike MCL-1 inhibitors that increase stability and prevent degradation of MCL-1, which triggers cardiotoxicity, CT-03p, a cereblon-based MCL-1 bifunctional degrader (Captor Therapeutics) does not affect non-human primate cardiac function in vivo at doses exceeding Degradation Dose 50 by over 100 times. Cardio-safety has been established by troponin I and D analyses and in the histopathological examination.

Aims

Investigate the therapeutic potential of CT-03p in AML cells, stem/progenitor cells, and AML cells resistance to venetoclax.

Methods

Viable cells and cell death were measured by flow cytometry after treated cells were stained with annexin V and 7-aminoactinomycin D in the presence of count beads. Protein levels were determined by Western blot and oxidative phosphorylation and fatty acid oxidation by Seahorse metabolic assays.

Results

MCL-1 degrader CT-03p effectively degraded MCL-1 and induced cell death in MV4-11 cells in vitro and in vivo in a MV4-11 xenograft mouse model. Additionally, CT-03p is highly active in MV4-11 cells with acquired resistance to venetoclax.
We observed that like venetoclax, CT-03p tends to be less active in TP53-mutant compared to TP53 wild-type (WT) cells. To assess the impact of TP53 status on CT-03p activity, we treated TP53 isogenic Molm13 cells with CT-03p and found that cells with TP53 defect are less sensitive to MCL-1 degrader compared to WT controls. Utilizing the hitherto sole targetable TP53-Y220C mutation model, we demonstrated that converting Y220C-p53 to p53-WT conformation by a p53-Y220C reactivator enhanced CT-03p activity in TP53-Y220C Molm13 cells, supporting p53 induces apoptosis and TP53 mutations impair efficacy of agents targeting BCL-2 proteins. Combination of CT-03p with venetoclax synergistically induced cell
death in CT-03p or venetoclax insensitive AML cell lines and AML blasts and/or stem/progenitor cells from patients with AML, even with TP53 mutations..
Metabolic analysis showed that CT-03p reduced oxidative phosphorylation and fatty acid oxidation in AML cells, which both contribute to venetoclax and chemotherapy resistance.

Summary/Conclusion

CT-03p degrades MCL-1, exerts antileukemia activities by inducing cell death and targeting metabolic activities, and overcomes venetoclax resistance in AML cells. TP53 mutations impair the efficacy of the MCL-1 degrader. Combination with venetoclax enhances CT-03p activities in venetoclax resistant and TP53-mutant AML cells and stem/progenitor cells. The importance of MCL-1 in therapy resistance and the lack of cardiotoxicity of CT-03p warrants future development of this degrader.