Abstract: P476

Title: AN ORAL COMBINATION THERAPY OF OR-2100 AND VENETOCLAX IN ACUTE MYELOID LEUKEMIA

Abstract Type: Poster Presentation

Session Title: Acute myeloid leukemia - Biology & Translational Research

Background:

The combination of hypomethylating agent (HMA) with venetoclax (Ven), a BCL-2 selective inhibitor has been the standard treatment for elderly patients with acute myeloid leukemia (AML). Because conventional HMAs, such as azacytidine (AZA) and decitabine (DAC), are not orally available, an oral HMA would be a suitable option for the combination therapy to reduce patients' burden on coming to hospitals. We have developed an oral HMA, OR-2100 (OR21), a 5'-O-trialkylsilylated of DAC, and reported it is a promising treatment for hematological malignancies (*Watanabe et al. Blood 2020, Ureshino et al. Mol Cancer Ther 2021, Kamachi et al. Cancer Letters 2022, Kurahashi et al. Blood Advances 2022*). Although oral AZA, CC486, and Oral DAC, ASTX727, are currently available in some countries, OR21 has the advantage that it is a single compound and less myelosuppressive. We are now conducting the Phase I trial to evaluate OR21 in Japanese patients with myelodysplastic syndrome. Here, we investigated the preclinical efficacy and mechanism of OR21 in combination with Ven for AML.

Aims:

To investigate the efficacy and mechanism of the combination therapy of OR21 and Ven for AML.

Methods:

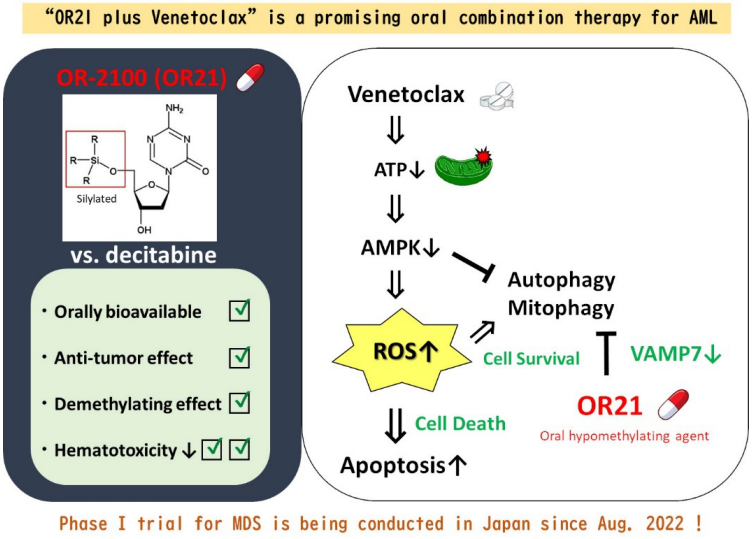
We investigated the efficacy of OR21 in combination with Ven against AML and analyzed the mechanism of the combination effect by comparing the transcriptome profile.

Results:

OR21 plus Ven inhibited cell growth, and increased apoptosis in AML cell lines (HL60, KG1a, SKM1, THP1, Kasumi-1) as comparable to DAC plus Ven or AZA plus Ven. We found that MCL-1 expression correlates inversely with sensitivity to OR21 plus Ven, but not to OR21 plus S63845, a selective MCL-1 inhibitor. OR21 plus Ven significantly prolonged survival or suppressed tumor growth in two different xenograft mouse models using AML cell lines (HL60 and KG1a). The differentially expressed gene analysis showed OR21 plus Ven significantly downregulated *VAMP7* expression, a member of the SNARE proteins, compared to Ven monotherapy in both HL60 and KG1a. HL60 with VAMP7 reduction with lentivirus represented attenuated cell growth and increased cell apoptosis. Furthermore, the lower *VAMP7* mRNA predicted favorable survival outcomes (dataset from TCGA) and higher Ven plus HMAs responses (dataset from *DiNardo CD et al. Blood 2020;135:791-803*) in patients with AML. Ven directory targets BCL-2 on mitochondria and VAMP7 regulates mitophagy/autophagy to maintain mitochondrial homeostasis by regulating reactive oxygen species (ROS). OR21 plus Ven increased ROS and ROS-induced apoptosis in HL60 and KG1a. Ven, as well as OR21 plus Ven, did not increase LC3 lipidation, an autophagy marker. Ven reduced AMP-activated protein kinase (AMPK) protein level, a master metabolic regulator, despite ATP reduction, leading to suppression of autophagy and increase of ROS accumulation. Meanwhile, Ven induced mitophagy and OR21 plus Ven increased ROS partially by attenuating Ven-induced mitophagy.

Summary/Conclusion:

Ven increased ROS with reduction of AMPK and suppression of autophagy. OR21 enhanced ROS accumulation with attenuated mitophagy response, leading to increased anti-leukemia effects. OR21 plus Ven is a promising oral combination therapy for AML.



Keywords: Hypomethylating agents, Reactive oxygen species, Venetoclax, Acute myeloid leukemia