(PS1742) ORAL HYPOMETHYLATING AGENT NTX-301 DEMONSTRATES POTENT ANTI-LEUKEMIC ACTIVITY AND ENHANCES RESPONSE TO VENETOCLAX IN CHRONIC MYELOMONOCYTIC LEUKEMIA (CMML)

Topic: 09. Myelodysplastic syndromes - Biology & translational research

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Background

Chronic myelomonocytic leukemia (CMML) is a clonal hematologic malignancy characterized by limited treatment options and suboptimal responses to currently available therapies, including hypomethylating agents and cytoreductive drugs. Novel therapeutic approaches are needed to improve disease control and reduce leukemic burden. NTX-301 is a novel oral hypomethylating agent with potential anti-leukemic activity, but its efficacy in CMML has not been characterized.

Aims

To evaluate the therapeutic activity of NTX-301 in primary CMML samples and in vivo CMML patient-derived xenograft (PDX) models, and to assess potential synergistic effects in combined drug therapy.

Methods

Primary CMML cells were cultured in cytokine-supplemented suspension assays and treated with NTX-301 alone or in comparison with clinically relevant agents including venetoclax, trametinib, decitabine, azacitidine, and hydroxyurea. Combination experiments were performed with NTX-301 and venetoclax. Cell viability, apoptosis, and differentiation were assessed by flow cytometry. IC_{50} values were calculated, and colony-forming cell (CFC) assays evaluated progenitor activity.
In vivo efficacy was investigated in two CMML-PDX models (Kloos et al. Leukemia 2020). Mice received vehicle, NTX-301, venetoclax, azacitidine, or NTX-301 plus venetoclax. Leukemic engraftment was monitored by serial measurement of human $CD45^+$ cells in peripheral blood and hematopoietic tissues. Survival, hematologic parameters, and differentiation marker expression were analyzed.

Results

NTX-301 inhibited primary CMML cell viability with IC_{50} values in the nanomolar to low micromolar range (23 nM to 1497 nM) and demonstrated greater potency than decitabine, venetoclax, azacitidine, trametinib and hydroxyurea, tested in parallel in 14 patient samples. Combination treatment with venetoclax resulted in synergistic effects in multiple patient samples, reflected by reduced IC_{50} values and enhanced inhibition in dose–response analyses.
NTX-301 induced apoptosis and promoted partial myeloid differentiation, as indicated by increased CD14 expression, while CD15 expression remained largely unchanged. In colony-forming cell (CFC) assays, NTX-301 significantly reduced colony formation across three independent primary CMML samples. In one CMML sample, combination treatment with venetoclax or trametinib further reduced progenitor growth compared to NTX-301 alone, whereas venetoclax or trametinib monotherapy showed no relevant effect.
In both CMML-PDX models, NTX-301 significantly reduced leukemic engraftment and prolonged survival compared with vehicle controls (median survival 118 vs. 241 days in model 1 and 122.5 vs. 216 days in model 2, vehicle vs NTX-301, respectively). Combination therapy with venetoclax enhanced inhibition of leukemic burden in peripheral blood, spleen and bone marrow, without further prolongation of overall survival compared with NTX-301 or azacitidine monotherapy or azacitidine plus venetoclax combination therapy. Increased CD14 expression during therapy suggested induction of differentiation in vivo.

Summary/Conclusion

NTX-301 demonstrates potent anti-leukemic activity in primary CMML cells and robust efficacy in two CMML-PDX models. The observed synergy with venetoclax and the consistent reduction of leukemic burden support further clinical development of NTX-301 as a promising therapeutic strategy for CMML.