(PB2694) INHIBITION OF LYSOSOMAL DETOXIFICATION AND RECYCLING PATHWAYS IN ACUTE MYELOBLASTIC LEUKAEMIA

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

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Background

Acute myeloid leukaemia (AML) remains an aggressive malignant blood disorder, with a 5-year survival rate of less than 30% and frequent relapses due to treatment-resistant leukaemic stem or progenitor cells. These cells survive chemotherapy, hypomethylating agents and targeted therapies by neutralising oxidative and aldehyde stress and recycling damaged components via cytoprotective autophagy. Although ALDHA1 inhibition affects a protective mechanism essential for cell survival, escape mechanisms exist, as evidenced by the possible development of resistant cell lines, the survival of cell populations identified in single-cell studies, and the existence of genes involved in resistance identified by the CRISPRcas9 approach, despite pharmacological inhibition of ALDHA1. the possible development of resistant cell lines, the survival of cell populations identified in single-cell studies, and the existence of genes involved in resistance identified by the CRISPRcas9 approach (unpublished data).

Aims

This invites us to evaluate the combination of ALDHA1 blockade with autophagy blockade.

Methods

We studied a series of AML cell lines (HL-60, KASUMI1, KG1, MONOMAC 6, MOLM14, MV-4-11, K562), cultured in the presence of an ALDHA1 inhibitor (Dimate), in the presence of an autophagy inhibitor (GNS561-Ezurpimtrostat), as well as the Azacytidine-Venetoclax combination, and by combining these various inhibitors

Results

Most of the cell lines tested proved to be sensitive to the autophagy inhibitor at concentrations compatible with in vivo use, as they were relatively comparable to the results obtained in clinical trials in hepatocellular carcinoma. A single-cell RNAseq study of 12 patient samples treated in vitro with the azacitidine-venetoclax combination shows a very significant increase in the number of cells expressing the PPT1, LC3, STINGn, P62, and MTOR genes, which are central elements of the autophagy mechanism. These data suggest that one of the mechanisms of escape from the azacytidine-ventoclax combination is the increase in the autophagy pathway, allowing both the elimination of toxic waste and the supply of energy to the leukemia cell. Preliminary data show synergy between GNS561 and both the ALDH inhibitor and the azacytidine-venetoclax combination, suggesting the possibility of blocking this therapeutic escape pathway.

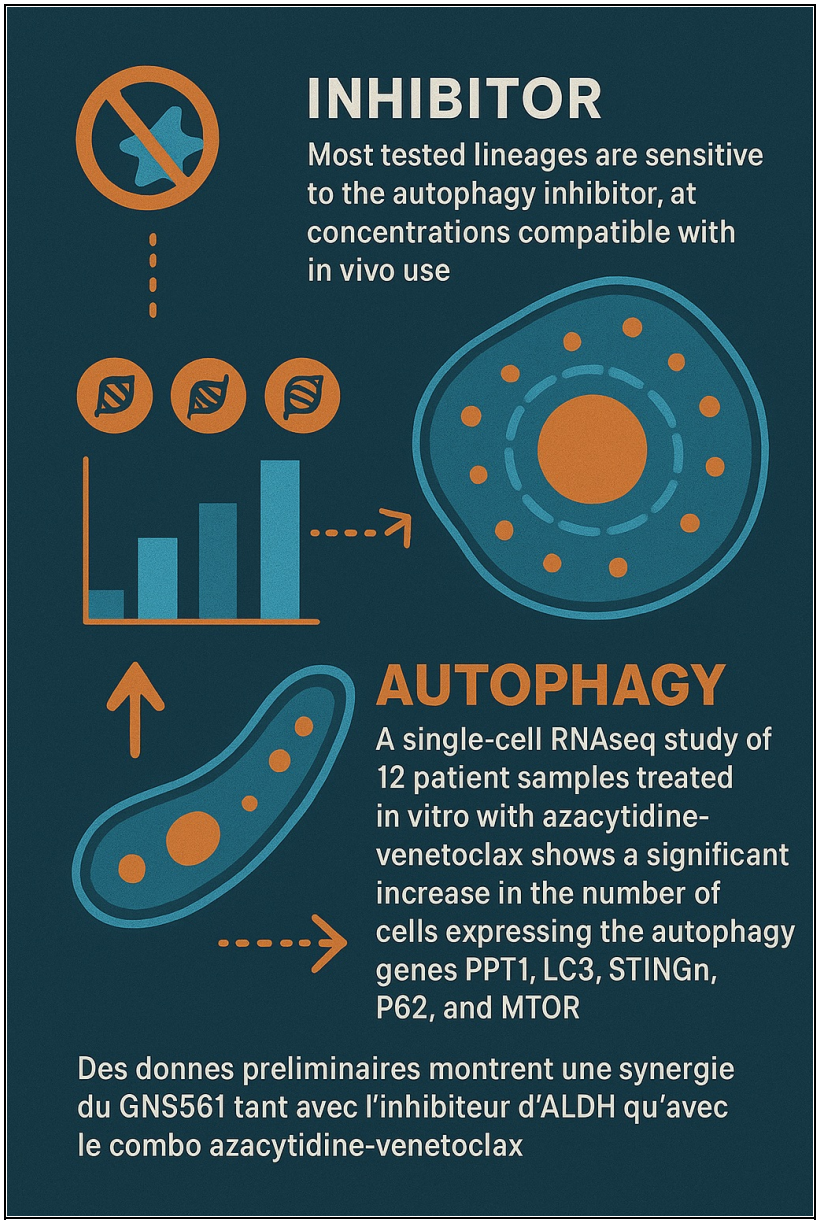
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Summary/Conclusion

Our preliminary data suggest that blocking the autophagy pathway suppresses a basic mechanism of leukemia cell survival as well as a mechanism of tumor escape from chemotherapy. These results will be supplemented by a study focusing on leukemia stem cells and identifying mechanisms of tumor escape from autophagy blockade, in particular by studying the effects of GNS561 on blasts from relapsed or refractory patients (SCALA clinical research protocol, Assistance Publique Hôpitaux de Marseille).
This study aims to lead to a phase II trial to demonstrate the efficacy of autophagy inhibition in AML using a combination of GNS561 with current treatments, particularly the azacytidine-venetoclax combination, while also evaluating the synergy of blocking the ALDH pathway in combination with the autophagy pathway.

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