(PB2705) SYNERGISTIC ANTI-LEUKEMIC ACTIVITY OF HOMOHARRINGTONINE AND SELINEXOR IN ACUTE MYELOID LEUKEMIA VIA DUAL INHIBITION OF THE C-MYC/MCL-1 PATHWAY

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

Weiguang Cui*[1], Liyuan Li[1], Mengying Zheng[1], Fan Yang[1], Lin Yang[1], Jianmin Luo[1]

[1]*Department of Hematology, The Second Hospital of Hebei Medical University, shijiazhuang, China;*

Background

Current therapeutic strategies for AML are hindered by drug resistance; although the HHT-selinexor regimen has been integrated into clinical practice for relapsed/refractory cases, its specific anti-tumor mechanisms have not been fully elucidated."

Aims

This study investigated the synergistic anti-leukemic potential of Homoharringtonine (HHT) in combination with the XPO1 inhibitor selinexor and elucidated the underlying molecular mechanisms

Methods

The effects of HHT and selinexor, as monotherapies and in combination, were evaluated in THP-1 and MOLM-13 AML cell lines. Cell viability was assessed using the CCK-8 assay, and synergistic effects were quantified by calculating the Combination Index (CI). Apoptosis was analyzed via flow cytometry (Annexin V/PI staining). The expression of key signaling proteins, including apoptotic markers (cleaved caspase-3, PARP-1), anti-apoptotic regulators (Bcl-xL, MCL-1), and the oncogene c-Myc, was determined by Western blotting.

Results

Both HHT and selinexor exhibited dose- and time-dependent anti-proliferative effects against AML cell lines as monotherapies. The combination of HHT and selinexor demonstrated potent synergy in inhibiting cell proliferation, with efficacy progressively enhanced by increasing drug concentrations and exposure duration. While both agents individually induced apoptosis, the combinatorial treatment significantly amplified apoptotic activation. At the molecular level, HHT and selinexor both targeted the c-Myc pathway; their combination resulted in a more pronounced suppression of c-Myc expression compared to either monotherapy, subsequently downregulating the downstream anti-apoptotic protein MCL-1. This was accompanied by increased cleavage of caspase-3 and PARP-1 and decreased expression of Bcl-xL.

Summary/Conclusion

The combination of Homoharringtonine and selinexor synergistically promotes apoptosis in AML cells by co-suppressing the c-Myc/MCL-1 axis and inhibiting anti-apoptotic regulators. These findings provide a mechanistic rationale for evaluating this combinatorial strategy as a promising therapeutic approach for patients with AML.