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617.ACUTE MYELOID LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Homoharringtonine Enhances the Anti-Leukemia Effect of Venetoclax in Acute Myeloid Leukemia with t(8;21)(q22;q22) Via Regulation of c-Myc/Bim Axis

Guopan Yu, MD PhD[1], *Zhao Yin*[1], *Zurong Yao*[1], *Xiaqi Nie*[1], *Hua Jin, MD*[1], *Yu Zhang*[1], *Dan Xu*[1], *Xuejie Jiang, MD*[1], *Baohong Ping*[1]

[1] Department of Hematology, Nanfang Hospital, Southern Medical University, Guangzhou, China

Purpose: Recently, small cases reports showed that acute myeloid leukemia (AML) with translocation (8;21)(q22;q22) [t(8;21) AML] responded poorly to venetoclax (VEN) plus azacitidine (AZA) (VA) regimen. Our previous study revealed homoharringtonine (HHT) enhanced the the killing effect of VA in AML. This study went further to explore the mechanism of VEN-resistance and the synergetic effect of VEN and HHT (VH) in overcoming resistance in t(8;21) AML.
Methods: Patients with/without t(8;21) AML, being treated with VA with/without HHT were included for response assessment. Synergetic effect and mechanism of VEN combined with HHT or AZA was studied in cell lines, primary cells and mice.
Results: Patients with t(8;21) AML acquired significantly lower CR/CRi rate than those without, with VA regimen as frontline (1/5 vs. 56/82, P=0.027) or salvage treatment (1/10 vs. 60/127, P=0.023), while the CR/CRi rate was comparable between the two cohorts with VA plus HHT (VAH) as salvage treatment (9/13 vs. 102/152, P>0.05). Synergetic effect in anti-leukemia was observed in VH but not VA in t(8;21) AML cell lines, primary cells and cell line-derived xenograft mice. Transcriptome RNA-sequencing and western blot detection found c-Myc and its downstring signialing were significantly decreased with the treatment of VH but not VA as compared to the controls. In addition, VEN induced accumulation of c-Myc in t(8;21) cells. Genetic silencing or pharmacological inhibition of c-Myc restored VEN sensitivity in t(8;21) cells. Co-immunoprecipitation assay found Bim, the crucial BH3-only protein, participated in the course of VH-inducing apoptosis. Direct or indirect inhibition of c-Myc increased expression of Bim, while overexpression of c-Myc significantly inhibited the transcription of Bim in t(8;21) cells. CUT&RUN assay revealed two functional sites of c-Myc binded to the promoter of Bim gene.
Conclusion: Abnormal activation of c-Myc might contribute to the resistance of VEN via suppression of Bim in t(8;21) AML. HHT might enhance the killing effect of VEN by regulation of c-Myc/Bim axis.
Key words: acute myeloid leukemia, t(8;21), homoharringtonine, venetoclax, c-Myc

Disclosures No relevant conflicts of interest to declare.

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