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POSTER ABSTRACTS

612.ACUTE LYMPHOBLASTIC LEUKEMIAS: CLINICAL AND EPIDEMIOLOGICAL

The Impact of ZNF384 Rearranged on Antigen Editing during Treatment-Specific Selective Pressures in Adult B Cell Acute Lymphoid Leukemia

Runxia Gu, MD[1], *Wenbin Liu, MD*[1], *Yihan Mei*[1], *Le Li*[1], *Chunlin Zhou*[1], *Yan Li, MD*[1], *Yuntao Liu*[1], *Shuning Wei*[1], *Dong Lin*[1], *Kaiqi Liu*[1], *Qiuyun Fang, MD*[1], *Xiaoyuan Gong, MD*[1], *Benfa Gong*[1], *Shaowei Qiu, MD*[1], *Bingcheng Liu, MD*[1], *Yingchang Mi, MD*[1], *Hui Wei, MD*[1], *Ying Wang*[1], *Jianxiang Wang, MD*[1]

[1] National Clinical Research Center for Blood Diseases, State Key Laboratory of Experimental Hematology, Haihe Laboratory of Cell Ecosystem, Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences &Peking Union Medical College, Tianjin, China

Objectives: Recent evidence shows that zinc finger protein 384 rearrangement (ZNF384r) was associated with the aberrant myeloid marker expression at diagnosis, which has been identified as a distinct subset of B cell acute lymphoid leukemia(B-ALL) related to an intermediate or even good prognosis during traditional therapy. However, there exists an indeterminate understanding of whether ZNF384r has a potential impact on antigen editing during treatment-specific selective pressures and shares the same prognostic significance in immunotherapy, such as chimeric antigen receptor T-cell therapy (CAR-T therapy).

Methods: In this study, we first evaluated the immunophenotype changes of 31 de novo adult B-ALL patients who harbor ZNF384r and received chemotherapy from Nov 2020 to May 2023. Then, 49 r/r B-ALL patients who received the CD19 or CD19/CD22-based CAR-T infusion in our institute were included in the analysis to further investigate the prognosis effects of ZNF384r on CAR-T therapy. At the same time, the next-generation sequencing and RNA sequencing data of the patients with ZNF384r were analyzed to explore the potential mechanisms behind it.

Results: First, we investigated the potential effects of ZNF384r in antigen editing after chemotherapy. Our results showed that 100% (31/31) of the patients express lymphoid lineage marker CD19 and 96.4% (27/28) of patients with CD22 expression at diagnosis. In addition, the majority of them had myeloid lineage marker expression, such as 96.2% (26/27) of patients with CD33 expression, and 96.5% with CD123 expression. After chemotherapy, 11 patients remained MRD positive after induction therapy, and 5 patients relapsed. In them, there were 18.8% (3/16) of patients lost CD19 expression, 12.5% of patients lost or reduced CD22 expression, while 100% of patients kept CD33 expression. For the adult r/r B-ALL patients who received the CD19 or CD19/CD22-based CAR-T infusion, there were 3 patients identified with EP300-ZNF384. Notably, all these three patients harboring ZNF384r relapsed within one year after the CAR-T therapy. Two of them experienced CD19-negative relapse, and one patient even had a myeloid transformation. These results indicated ZNF384r might associate with antigen editing during treatment-related selective pressures.

The next-generation sequencing was performed in 25 B-ALL patients harboring ZNF384r before chemotherapy or CAR-T therapy, the results showed that in addition to CREBBP, NRAS, ETV6, NOTCH1/3, FLT3-ITD mutation was also the most common co-mutation with ZNF384r. Furthermore, the transcriptome analysis showed the Jak-STAT signaling pathway and the hematopoietic cell lineage pathway were highly enriched in the group with EP300::ZNF384 fusion compared with TCF3::PBX1 fusion. The expression of CD33, CD34, CD123, and IL5 were also significantly up-regulated in the EP300::ZNF384 group. All these results indicated ZNF384r might be involved in the regulation of the hematopoietic cell lineage differentiation pathway and myeloid lineage skewing.

Conclusions: Our findings demonstrated that ZNF384 rearrangement might induce antigen editing during treatment-related selective pressures in adult B cell acute lymphoid leukemia, especially in CAR-T therapy. More efforts are needed to reveal mechanisms behind it to help reduce antigen loss and relapse rate after CAR-T therapy.

Disclosures No relevant conflicts of interest to declare.

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