Abstract: P383

Title: THE NEXT-GENERATION SEQUENCING (NGS) BASED MRD ASSESSMENT COULD BETTER PREDICT RELAPSE THAN MULTIPARAMETER FLOW CYTOMETRY (MFC) IN ADULT B-CELL ACUTE LYMPHOBLASTIC LEUKEMIA

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Background:

Positive minimal residual disease detected by multiparameter flow cytometry (MFC-MRD) was consider a parameter to identify patients at high risk for relapse in B-cell acute lymphoblastic leukemia (ALL). However, MFC-MRD negative patients also relapse. Therefore, more sensitive and accurate techniques are urgently needed to further identify high-risk patients with recurrence, especially in patients with negative MFC-MRD.

Aims:

To explore a MRD detection technique with higher sensitivity and relapse predictive power.

Methods:

In this study, we enrolled 93 B-cell ALL patients with paired bone marrow (BM) samples at diagnosis and after 2 cycles of consolidation chemotherapy. All of the patients were identified with dominated clonotypic rearrangements in the diagnostic BM DNA samples by a next-generation sequencing (NGS)-MRD assay (Seq-MRD®, Genetron Health), which detect the rearranged IgH-VDJ, IgH-DJ, IgK, and IgL sequences. NGS -MRD was subsequently measured at the end of two courses of consolidation therapy by tracking the identified clonotypic rearrangements at the sensitivity thresholds of 10^{-7}. Paired MRD results were compared between NGS and multiparameter flow cytometry (MFC, sensitivity 10^{-4}). The relapse predictive power between them was also compared by measuring the relapse free survival (RFS) of the enrolled patients.

Results:

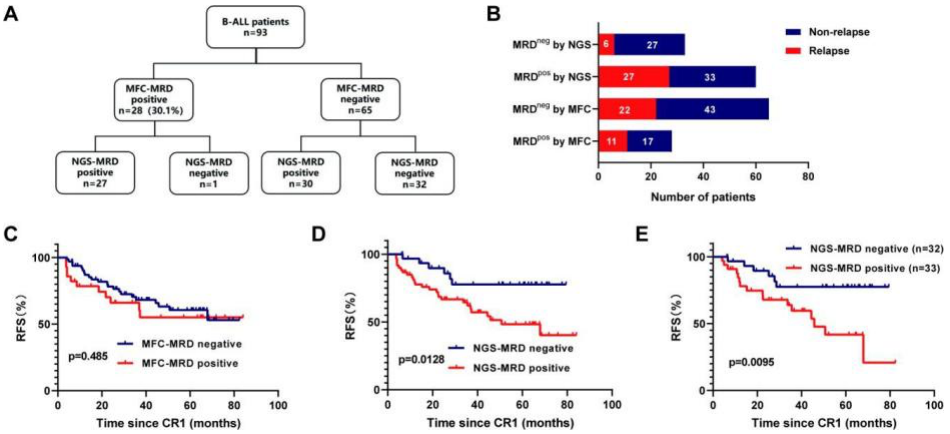
Sixty-five (69.9%, 65/93) patients were MFC-MRD negative after two cycles of consolidation chemotherapy while 33.8% (22/65) relapsed during the follow-up (Figure A- B). This subgroup was further divided into NGS-MRD positive (50.8%, 33/65) and NGS-MRD negative (49.2%, 32/65). The overall MRD negativity rate by NGS was

35.5% (33/93), and the relapse rate of the NGS-MRD negative patients was 18.2% (6/33). There was no significant difference in RFS between MFC negative and MFC positive patients (p=0.0485, Figure C). However, NGS-MRD negative patients showed a significantly better RFS than NGS-MRD positive patients (p=0.0128, Figure D). Besides, the RFS of the MFC-MRD negative patients could be further stratified based on the NGS-MRD results. The patients who were MRD negative by both MFC and NGS had a better RFS that those who were MFC-MRD negative but NGS-MRD positive (Figure E).

Summary/Conclusion:

As a promising methodology with superior sensitivity, deep NGS could refine the relapse predictive ability by reducing the false negative rate in MFC-MRD. The powerful relapse risk predictive value of NGS will assist physicians to further identify high-risk patients, especially in MFC-MRD negative.

Figure.



(A) The results of MFC-MRD and NGS-MRD in the 93 patients (B) Clinical outcome of 65 MFC-MRD negative patients and their corresponding MRD status by NGS. (C) Relapse-free survival analysis based on the MFC-MRD results in the 93 patients. (D) Relapse-free survival analysis based on the NGS-MRD results in the 93 patients. (E) Relapse-free survival analysis in 65 MFC-MRD negative patients by NGS-MRD status.