

News Release

Title

Clinical utility of next-generation sequencing-based minimal residual disease in pediatric B-cell acute lymphoblastic leukemia

Key Points

- 1. We established a highly sensitive minimal residual disease (MRD) detection using next-generation sequencing (NGS) in childhood acute lymphoblastic leukemia.**
- 2. NGS-based MRD provided more accurate prediction of prognosis than that based on conventional methods such as real-time quantitative PCR.**
- 3. The better prediction of prognosis by NGS-based MRD will enable more precise treatment strategy leading to improved prognosis.**

Summary

Emeritus Prof. Seiji Kojima (corresponding author), Hideki Muramatsu, and Yuko Sekiya (first author) at Department of Pediatrics, Nagoya University Graduate School of Medicine (Dean: Masahide Takahashi, M.D., Ph.D.) assessed the clinical utility of next-generation sequencing (NGS)-based minimal residual disease (MRD) detection in pediatric B-cell acute lymphoblastic leukemia (ALL).

ALL is the most frequent cancer in childhood. Stratified therapy based on individual risk assessment is known to improve the clinical outcome. MRD, which refers to residual tumor (leukemic) cells after treatment, strongly predicts the risk of relapse in patients with ALL. MRD detection was conventionally performed using flow cytometry or real-time quantitative PCR methods. However, NGS-based measurement was suggested to provide a more sensitive method. In this study, we assessed the clinical utility of NGS-based MRD detection in a cohort of pediatric ALL.

NGS-based measurement was found to be sensitive to detect one tumor cell in one million cells (10^{-6} sensitivity), while conventional methods detected one in 10 thousand to one in 100 thousand (10^{-4} to 10^{-5} sensitivity). By studying 72 patients with B-cell ALL, the presence of MRD at day 33, 80, 4-5 months, and after completion of therapy was found to strongly predict prognosis.

This study demonstrated the potential superiority of the NGS-based method over conventional methods. Risk assessment and subsequent optimized therapy using NGS-based MRD will improve the treatment outcome in patients with ALL.

Background

Acute lymphoblastic leukemia (ALL) is the most frequent cancer in childhood, occurring in approximately 600 children per year in Japan. Stratified therapy, improved combination of anti-cancer drugs, and introduction of hematopoietic stem cell transplantation (including bone marrow transplantation) significantly improved the treatment outcome, reaching 80-90% long-term survival. However, patients with relapsed or refractory ALL still have poor prognosis.

The remaining cancer cells after treatment (called minimal residual disease; MRD) is among the strongest predictor of prognosis in ALL. Furthermore, the intensification of treatment based on the presence of MRD is known to improve patients' clinical outcome. MRD was conventionally measured by flow cytometry (FCM) and real-time quantitative polymerase chain reaction (RQ-PCR). However, these methods are time

consuming, laborious, and require experienced technicians. Therefore, not all patients with ALL were measured for MRD in Japan. A previous basic study suggested that a next-generation sequencing (NGS)-based measurement provides a more convenient and sensitive method of MRD detection. In this study, we studied 72 patients with childhood ALL to test the hypothesis that an NGS-based method provides more sensitive MRD detection and therefore more accurate prediction of prognosis.

Results

We studied 72 patients with childhood ALL (age, 0-15 years). We measured MRD using 232 samples obtained at day 33, 80, 4-5 months, and after completion of therapy.

NGS-based measurement was found to be sensitive to detect one tumor cell in one million cells (10^{-6} sensitivity), while conventional methods detected one in 10 thousand to one in 100 thousand (10^{-4} to 10^{-5} sensitivity).

Firstly, we assessed the clinical utility of NGS-based MRD using data at day 33 and day 80 after diagnosis (Figure 1). We classified patients into standard risk (patients without MRD at both day 33 and 80) and intermediate risk (patients with MRD at day 33, 80 or both). While patients with standard risk had 100% chance of 5-year survival without relapse, patients with intermediate risk had significantly inferior prognosis (62%, $p < 0.01$).

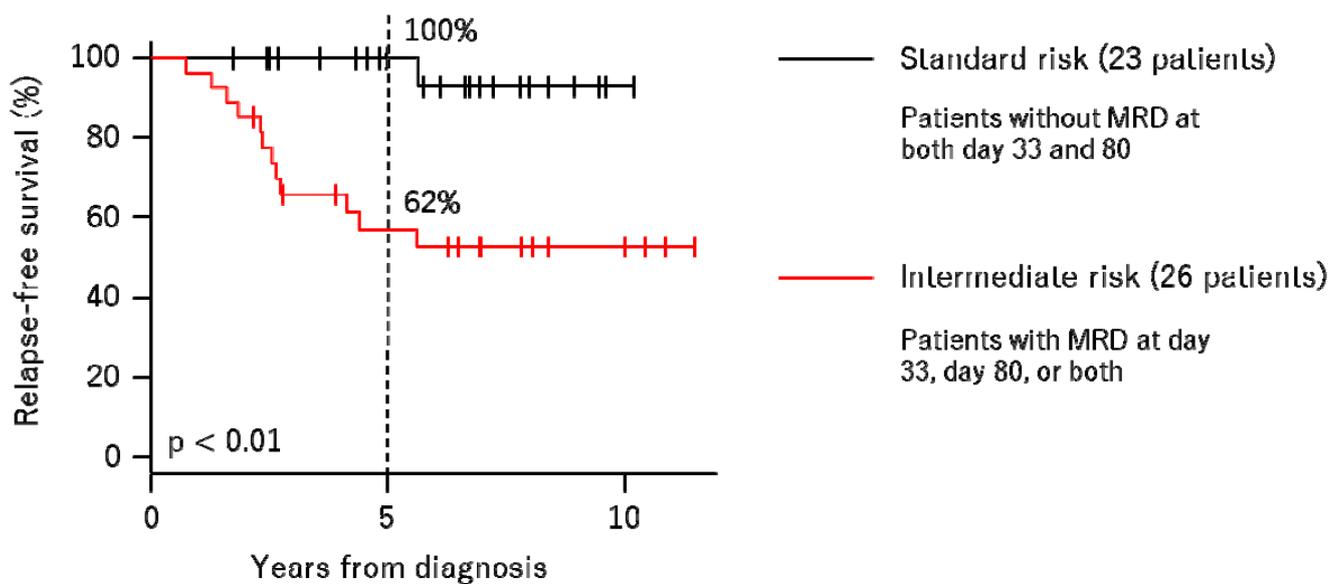


Figure 1. Risk stratification based on MRD status at day 33 and 80

Patients were stratified into standard and intermediate risk based on NGS-based MRD status at day 33 and 80. X and Y axes indicate years from diagnosis and percentage of survival without relapse, respectively.

Secondly, we assessed the results obtained at 4-5 months after diagnosis and at the time of completion of therapy (Figure 2). Conventional methods detected MRD only in a small fraction of patients in these time points, possibly because the continuing treatments decrease the number of leukemic cells to undetectable level. However, we detected NGS-based MRD in 11 out of 58 patients (19%) and 4 out of 54 patients (7.4%) at 4-5 months and after completion of therapy, respectively. Furthermore, patients with MRD at these time points had significantly inferior relapse-free survival (41% and 25%) compared with 98% in patients without MRD. In particular, all of the patients carrying MRD at the completion of therapy relapsed. These results

suggest that, NGS-based detection is able to detect MRD at these time points and the MRD positivity strongly predicts relapse.

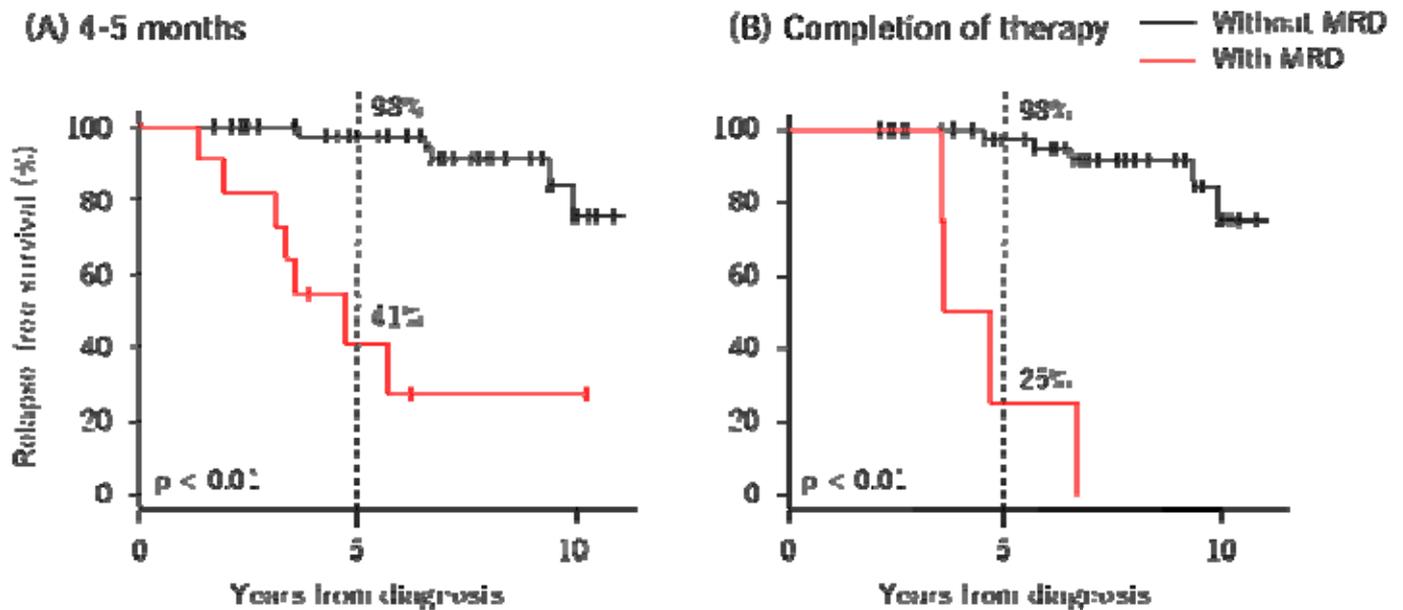


Figure 2. Relapse risk based on MRD at 4-5 months and the time of completion of therapy
These panels show the relapse-free survival of patients stratified by the positivity of MRD at 4-5 months (A) and the time of completion of therapy (B).

Summary and Future Perspective

This study demonstrated the potential superiority of the NGS-based method over conventional methods. Risk assessment and subsequent optimized therapy using NGS-based MRD will improve the treatment outcome in patients with ALL.

Publication

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