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REVIEW ARTICLE

Minimal Residual Disease Measurement in Acute Lymphoblastic Leukemia

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ABSTRACT
Acute lymphoblastic leukemia (ALL) is an aberrant transformation of a single precursor B or T lymphocyte resulting in an uncontrolled proliferation in the bone marrow, blood, and extramedullary tissues. Despite the increasing rates of complete remission and overall survival, the risk of relapse with a poor rate of survival is still high. This rate of relapse might be owing to the inaccuracy of the conventional risk factors, including age, white blood cell count, immunophenotype, and cytogenetics in predicting the initial therapy response and the overall outcome. The introduction of minimal residual disease (MRD) measurement in the last decades has an obvious impact on the prognosis and the management of ALL. MRD assessment has shown to be the most powerful indicator of the response to therapy and relapse risk. Likewise, it is an independent factor for the overall outcome of various ALL patient age groups. While its negativity is highly associated with long event-free survival, MRD positivity is associated with short event-free survival. Interestingly, MRD assessment has changed ALL risk group stratification, and it can be measured using ALL cells immunophenotypic features, the expression of fusion genes, and immunoglobulin (IG) and T-cell receptor (TCR) clonal rearrangement. MRD measurement determines ALL remission more accurately and before it can be detected by traditional morphologic assays. Additionally, MRD assessment is one of the most important tools to develop personalized therapy for ALL.
Keywords ALL, MRD, Prognosis, immunophenotype, Gene fusion, IG/TCR

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INTRODUCTION

Acute lymphoblastic leukemia (ALL) is a malignant transformation and uncontrolled proliferation of precursor B or T lymphocytes in the bone marrow (BM), blood and extramedullary tissues [53]. It consists almost 80% of pediatric leukemia though it is a rare disorder. B cell acute lymphoblastic leukemia (B-ALL) is more common than T cell acute lymphoblastic leukemia (T-ALL), comprising 85%-90% of pediatric ALL and 75% of adult ALL, although B- lymphoblastic lymphoma is less common than T-lymphoblastic lymphoma, comprising 10-15% of all lymphoblastic lymphomas [18, 51]. The first peak of ALL incidence occurring in early childhood and the second peak of the incidence occurring at late adulthood, around the age of 50 [45].

Current chemotherapeutic treatment strategies, including induction, post-induction and maintenance therapy are highly efficient in ALL. The cure rate of pediatric B-ALL is > 90% and the 5–year event free survival is > 85% for almost all clinical risk groups [50, 35]. Likewise, the 5-year event free survival of pediatric T-ALL reached > 90% [60, 31]. In spite of these promising statistics, an increase risk of relapse in patients with the poor prognosis is remained. Though the conventional risk factors, including age, white blood cell count, immunophenotype, and cytogenetics are crucial during the initial diagnosis, none are accurate in predicting response to initial therapy and overall outcome.

MRD MEASUREMENT RELIABILITY IN ALL

MRD measurement in ALL is proving to be the most reliable indicator of therapy response and relapse risk among other major risk factors, including age, white blood cell count, time to complete remission (CR), immunophenotype and genotype [57]. Additionally, MRD measurement has a valuable impact on the survival after the diagnosis of ALL in children and adults [13-15]. Therefore, MRD measurement has been used in several large tail studies as a prognostic parameter aiming to improve the therapy outcome [24, 25, 33, 27]. Analogously, MRD assessment becomes standard practice in evaluating ALL therapy. For example; it was reported that the MRD absence is essential for all age groups of ALL patients. These findings were consistent across the treatment, techniques and times of MRD evaluation, risk group stratification and cutoff levels [5,11]. Additionally, the molecular MRD failure in adult ALL patients was associated with a high relapse risk and significant poor overall survival [30]. In pediatric ALL, MRD positivity at any time point was significantly associated with the incidence of relapse and short event-free survival in all risk group stratification comparing to MRD negativity [6, 7, 21, 22]. Interestingly, molecular quantification of MRD sub-classified the homogeneous standard risk ALL group into three risk groups called low risk, intermediate-risk and high risk groups with relapse rates of 0%, 47% and 94%, respectively, based on the level of the detected MRD at various follow-up time points [7, 10]. Regardless the other major risk factors, the detectable levels of MRD during remission induction and consolidation treatment was the most significant prognostic indicator on ALL [46, 47, 9]. Of note, the molecular MRD failure populations were identified as a new poor prognosis group [30]. In Philadelphia chromosome-positive ALL patients, MRD monitoring may guide the treatment intensification in first CR [49]. In children with B-precursor ALL, intensive treatment in MRD positive patients with methotrexate or dexamethasone did not overcome the high risk prognostic information of MRD but it altered the relapse time [8]. MRD negativity may lead to the treatment reduction in clinical standard-risk and intermediate-risk patients according to UKALL2003 trail [57]. However, MRD positivity before umbilical cord blood transplantation predicted high risk of relapse and a short event-free survival [1].

MRD AS AN INDEPENDENT PROGNOSTIC MARKER IN ALL

MRD measurement is an independent prognostic factor in pediatric and ALL. For example, the persistence of MRD at week 14 of continuation therapy was an independent high-risk relapse indicator on children with ALL [18]. Additionally, in children poor prognosis precursor B-ALL, MRD assessment by real-time polymerase chain reaction (PCR) and flow cytometry showed independent prognostic information in multivariate analysis [37]. Independently from clinical risk groups, absolute MRD quantification by flow cytometry was a strong and independent prognostic marker in pediatric ALL [23]. It was also reported that MRD quantification by PCR was an independent indicator for relapse-free survival in children underwent to ALL-BM treatment protocol [40]. Likewise, in a mixed group age study treated according to trail ALL-REZ BFM P95/96, the molecular assessment of MRD in the post induction period was the strongest independent prognostic marker for event-free survival in intermediate risk relapsed group [25]. In addition, in children and adolescents B-cell precursor ALL patients treated according to AIEOP-BFM ALL 2000, MRD assessment by PCR showed an independent prognostic information on top of other prognostic markers [17].

Likewise, MRD quantification is an independent prognostic factor in adult ALL. For instance, in Philadelphia chromosome-positive ALL patients underwent to imatinib treatment and allogenic transplantation, the molecular CR was the most significant indicator for long-term transplantation outcome in multivariate analysis [39]. Using MRD assessment in NILG-ALL 09/00 protocol improved risk definitions and showed its significance to guide post-consolidation therapy or stem cell transplantation [2]. In addition, multivariate analysis during consolidation treatment showed that bone marrow MRD negativity at day 35 was the most correlated independent prognostic factor for adult ALL [56]. Molecular MRD failure in B-cell Philadelphia-negative ALL was a strong indicator for treatment failure in patients treated with UKALL XIILECOG2993 protocol [44]. In T-cell and B-cell precursor ALL, oncogenetic markers and MRD levels were strongly and independently associated with high-risk of relapse and shorter event-free and overall survival [4, 58].

MRD MARKERS IN ALL

ALL cells can be distinguished from healthy lymphocytes by their immunophenotypic features, the expression of fusion genes, and immunoglobulin (IG) and T-cell receptor (TCR) clonal rearrangement. The quantification of these markers can be conducted using peripheral blood and/or BM samples. Nevertheless, in B-cell precursor acute lymphocytic leukemia (BCP-ALL) the preferred sample is BM due

to the low levels of MRD in peripheral blood [19, 54]. Hence, BM samples might be fundamental in BCP-ALL, but not in T-ALL.

Immunophenotypes

ALL cells express unique antigen receptors that simplify the recognition of their type as B- or T-progenitors [14]. The presence of T-cells carry the immunophenotypic features of T-cell progenitors in the peripheral blood or BM is enough to recognize T-lineage ALL as T-cell progenitors remain in the thymus and do not migrate. The B-cell precursors lodge in the BM, but are frequently disappear during the first three weeks of induction therapy, due to their high susceptibility to chemotherapy. Therefore, B-cell precursor markers can be enough for treatment response evaluation [19]. However, additional cell markers are needed to be applied to distinguish healthy and leukemic B cells after induction therapy.

In addition, ALL cells express cell markers differentiate them from their normal counterparts. These immunophenotypic characteristics are called leukemia-associated immunophenotypes (LAIP). LIAP is sub-classified into two categories. Firstly, LIAP resulted from fusion proteins that originated form chromosomal translocations. For instance; BCR-ABL1 fusion protein that attributed to the reciprocal translocation t(9;22)(q34;q11), which occurs in 2%-4% of childhood ALL and 25% of adult ALL [32, 34, 35]. Likewise, MLL-AF4 that caused by the chromosomal translocation t(12;21)(p13;q22), which can be found in 2-6% of pediatric ALL [46, 45]. Additionally, TELL-AML1 (ETV6-RUNX1) which is the most frequent translocation in pediatric ALL, occurs in 20-25% of all childhood chromosomal translocation [62]. Also, the E2A-PBX fusion protein which occurs in 4-8% of pediatric ALL [59, 60]. Secondly, LIAP that normally found during lymphopoiesis, but are expressed in an aberrant manner in ALL. These immunophenotypes are widely used to assess MRD in ALL using multi-parameter flow cytometry. For example; CD73 and CD86 that show relativity to BCP-ALL [52]. In addition, Galectin-1 found to be a reliable MRD marker of MLL-rearranged B-ALL [36]. Twenty-two CD markers were reported to be differentially expressed in B-cell leukemia and can be appropriate MRD markers by multi-parameter flow cytometry, including CD44, BCL2, HSPB1, CD73, CD24, CD123, CD72, CD86, CD200, CD79b, CD164, CD304, CD97, CD102, CD99, CD300a, CD130, PBX1, CTNNA1, ITGB7, CD69, and CD49f [21, 22].

Gene Fusions

ALL cells can be distinguished from normal cells by their genetic abnormalities. The most common genetic aberrations used for MRD measurement are *BCR-ABL1*, *TCF3-PBX1*, *TELL-AML1*, and *MLL-AFF1* [26, 55]. In addition, gene fusions requiring CRLF2 that is found in approximately 15% of adult ALL and in poor prognosis childhood B-cell ALL, and in almost 50% of ALL concordant with Down syndrome is a potential MRD marker [43, 61]. Recurrent aberrations that can be used for routine MRD measurement are present in almost 40% of adults and children with ALL [11].

IG/TCR gene rearrangement

Duringthe development of B cells, the different segments of IG genes are reorganized resulting in a distinctive gene sequence. Likewise, TCR genes undergo specific rearrangement in T-cell progenitors. ALL cells have clonal IG/TCR gene rearrangement that can be applied for differentiating ALL cells from their normal counterparts as ALL cells urge from an oncogenic transformation of a sole lymphoid progenitor [13-15]. While IG rearrangement is prevalent in B-cell ALL, TCR gene rearrangement is prevalent in T-cell ALL. TCR gene rearrangement also were reported in 90% of B-cell ALL, and IG gene rearrangement were reported in 20% of T-cell ALL [12].

The MRD measurement time point

MRD significance is based on the time point of the assessment. MRD prognostic values vary according to time points of the measurement. Individuals with the favorable prognosis and the low risk of relapse show early MRD clearance. However, the persistence of MRD at the end of post-induction therapy is correlated with the unfavorable prognosis and high risk of relapse.

In childhood ALL, MRD levels of ALL patients were measured at days 7, 8, 14, and 15 of induction therapy [16, 28, 38, 41, 42]. MRD levels at day 8 and day 29 of induction therapy in peripheral blood and BM, respectively, of PBC-ALL were associated with event-free survival (EFS). The probability of EFS in individuals showed MRD negativity was 88%, whereas the probability in MRD-positive patients was 59% [6]. MRD levels in BM stratified pediatric ALL patients into three groups: favorable (< 0.1% blast cells), intermediate (0.1 to < 10% blast cells), and the poor prognosis (≥ 10% blast cells), with 7.5%, 17.5%, and 47.2% 5-year cumulative relapse incidence, respectively [3].

In adult ALL, most of the large trail groups assessed MRD levels after the end of induction and/or during early post-induction therapy. For example, the GMALL trail group showed an association between MRD negativity after induction-2 and/or post-induction-I and treatment responses regardless of pre-therapeutic risk stratifications [48]. However, MRD positivity after consolidation-I classified individuals with molecular failure as a new poor prognosis group [10, 29].

CURRENT ISSUES OF MRD APPLICATIONS

Despite the evolution of ALL diagnosis and management that were made after applying MRD diagnosis, many limitations of MRD are still to be resolved. For example, the availability of MRD assessment techniques is limited to specialized centers. Additionally, unifying the current method standardization for MRD evaluation is urgently needed as the discrepancies between widely used methods, flow cytometry and PCR, is apparent. The sensitivity of MRD determination assays is questionable since the early relapse of ALL in MRD negative cases was found and a long EFS was reported in MRD positive cases. The determination of the MRD negativity is debated owing to the difference in utilized techniques and their sensitivity levels. The cellularity limitation of the samples is another difficulty in MRD detection as the BM is the preferred current sample, particularly in the BM regeneration period and in plastic BM. The time point of MRD measurement is needed to be determined since different trial groups applied different time points.

CONCLUSION

MRD assessment allows to determine ALL remission more accurately than the conventional morphologic assays. MRD levels at early time points determine cases with the promising treatment response and may guide the treatment intensity. Likewise, the significant association between MRD levels and therapy outcome was proven by several studies and its independent prediction of the outcome was shown. Additionally, MRD renders the early detection of ALL relapse before it can be detected by morphologic techniques. It is usefulness to assess new drug efficacy was approved by large trail groups. Finally, MRD measurement may pave the road to the development of personalized therapy for ALL patients.

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COMPETING INTEREST

The author declared that no competing interest exists.

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