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REVIEW

Clinical Value of Measurable Residual Disease in Acute Lymphoblastic Leukemia

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Abstract: Measurable (minimal) residual disease (MRD) status in acute lymphoblastic leukemia (ALL) has largely superseded the importance of traditional risk factors for ALL, such as baseline white blood cell count, cytogenetics, and immunophenotype, and has emerged as the most powerful independent prognostic predictor. The development of sensitive MRD techniques, such as multicolor flow cytometry (MFC), quantitative polymerase chain reaction (PCR), and next-generation sequencing (NGS), may further improve risk stratification and expand its impact in therapy. Additionally, the availability of highly effective agents for MRD eradication, such as blinatumomab, inotuzumab ozogamicin, and chimeric antigen receptor (CAR) T-cell therapies, enabled the development of frontline regimens capable of eradicating MRD early in the treatment course. While long-term follow-up of this approach is lacking, it has the potential to significantly reduce the need for intensive post-remission treatments, including allogeneic bone marrow transplantation, in a significant proportion of patients with ALL.

Keywords: acute lymphoblastic leukemia, minimal residual disease, multicolor flow cytometry, polymerase chain reaction, next-generation sequencing

Introduction

The utilization of multi-agent chemotherapy has significantly improved outcomes in adult patients with acute lymphoblastic leukemia (ALL). Most patients achieve complete remission (CR) after standard induction chemotherapy; however, relapses are common. These relapses are caused by the persistent leukemic blasts resistant to cytotoxic chemotherapy and remain the primary cause of mortality in patients with ALL.[1] Present at low levels during remission, residual leukemic blasts are usually undetected by morphological examination. However, with the use of multiparameter flow cytometry (MFC) and polymerase chain reaction (PCR), the residual disease can be detected in approximately 30–50% of cases that achieve CR.[1–3] Persistent leukemic cells in the setting of remission are referred to as measurable (minimal) residual disease (MRD), which defines the remaining disease burden after therapy.[1]

MRD has become an essential prognostic tool for all ALL subtypes, including B-cell (Philadelphia chromosome-positive or negative) and T-cell lineages.[4,5] Across all treatment regimens and methods of MRD evaluations, the detection of MRD after therapy correlates with worse disease-free survival (DFS) and overall survival (OS). In addition to its prognostic significance, MRD status can impact treatment decisions by guiding therapy to include MRD clearing regimens such as blinatumomab and suggesting or avoiding subsequent consolidation approaches without allogeneic stem cell transplantation (ASCT). Although MRD timing and evaluation are well established in pediatric ALL, the MRD status already guides treatment intensity and decision-making regarding (ASCT), MRD's optimal timing and effect in adult ALL remain to be determined. This review will discuss the assessment, management, and prognostic role of MRD in adult patients with ALL.

Assessment of Measurable Residual Disease

Several laboratory techniques have been validated to detect and quantify MRD in ALL. MFC and quantitative PCR by the analysis of recurrent gene fusions (eg, BCR/ABL1) or rearranged immunoglobulin (IG) or T-cell receptor (TCR)

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genes are the most used techniques.[6] However, more sensitive, and specific MRD techniques have also been developed, such as high throughput next-generation sequencing (NGS) and droplet digital PCR. In Figure 1, we summarized the advantages and disadvantages of the commonly used MRD techniques.

Multiparametric Flow Cytometry

MFC is a fast and relatively cheaper technique that applies to most ALL cases. Test results are frequently finalized within 1–5 days, depending on the laboratory. Standard of care MFC assays can identify the persistent leukemic cells at the level of 10^{-4} (1 out of 10,000 nucleated cells) sensitivity by analyzing aberrant leukemia-associated immunophenotypes (LAIPs), including aberrant expression of myeloid antigens or altered density of antigens commonly expressed on benign lymphoid precursors.[1] Use of ≥8-color flow cytometry assays allows for the analysis of the expression of more antigens.[7–9] Compared with standard MFC (3–4 color assay) flow cytometry, ≥8-color flow cytometry increases the diagnostic accuracy.[7–9]

By one MFC-based approach, all LAIPs identified on leukemic cells at diagnosis are analyzed during treatment and count as MRD if they are still detected in the remission samples.[1] However, the immunophenotypic shift can arise because of treatment which can compromise the accuracy of this method (comparing LAIPs between diagnostic and remission), potentially resulting in false-negative MRD assessments.

Another MFC-based methodology called the "different from normal" (DfN) approach detects the difference in immunophenotypes observed in remission samples as compared with normal immunophenotype distribution.[10] Thus, MRD may be analyzed without the need for an initial diagnostic sample or irrespective of immunophenotypic shift throughout therapy.[6,10] However, there may be less diagnostic certainty with DfN approach, and therefore in most laboratories where this approach is practiced, baseline LAIPs are used for comparison (when baseline sample available). Some groups, such as European Leukemia Network, have advocated using an integrated "LAIP-based DfN" approach to evaluate MRD.[11] Irrespective of the specific methods used, the lack of uniformity between laboratories and pathologists has been one of the important limitations of MFC for MRD assessment.[1] Furthermore, analyzing antigen expression

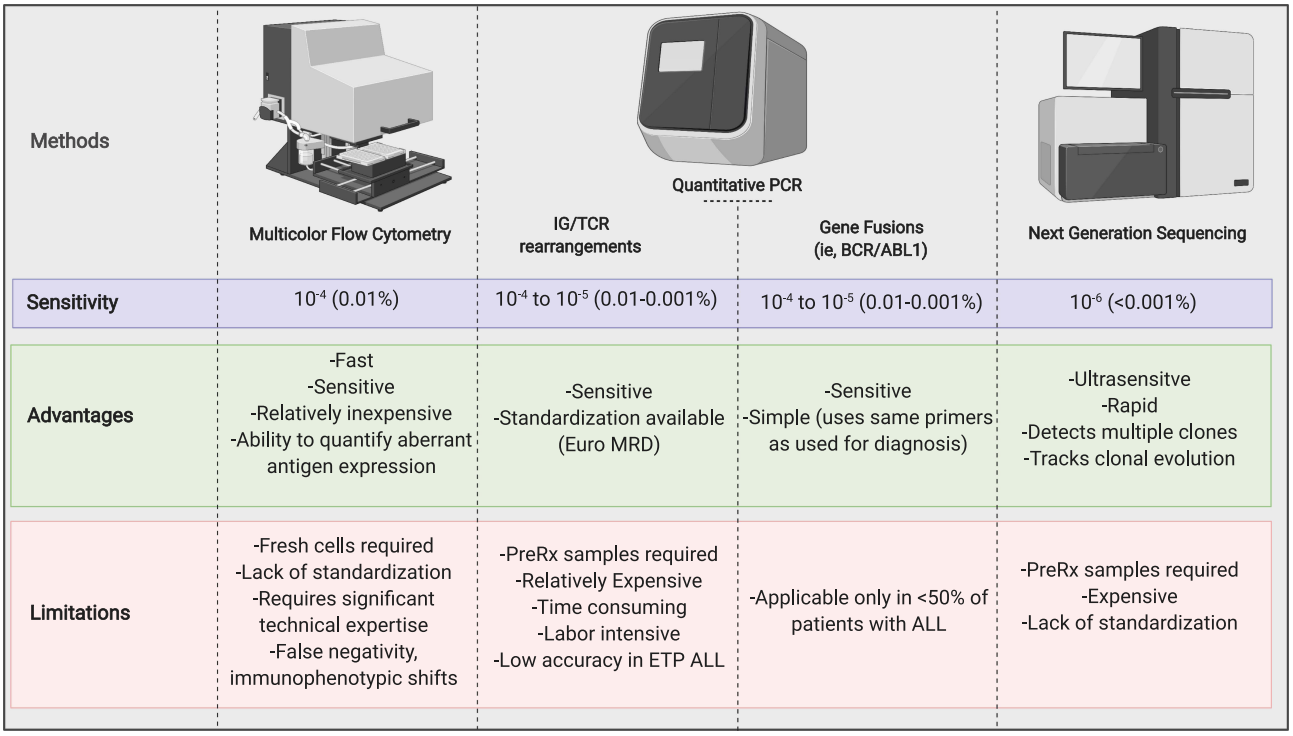

Figure 1 Measurable Residual Disease Assessment Methods.
Note: Created with https://BioRender.com.
Abbreviations: IG/TCR, immunoglobulin and T-cell receptor; Pre-Rx, before treatment.

patterns and maturation of normal hematopoietic precursors in resting and regeneration states and interpreting the resultant data require significant expertise and knowledge, especially when the DfN approach used.

Real-Time Quantitative PCR

Real-time quantitative PCR (RQ-PCR) is a highly sensitive methodology that is used to detect and quantify MRD in ALL. In Ph-negative B-cell ALL and T-cell ALL, rearranged immunoglobulin IG or TCR genes, and in Ph-positive ALL, BCR-ABL1 mRNA transcripts are the predominantly chosen MRD targets for PCR.[12,13] Other gene fusion involving *CRLF2* or *MLL* might be utilized as targets in other ALL subtypes; however, there is limited clinical evidence to support their use as MRD indicators.[1] Although methodologies are different, MFC and RQ-PCR assays result in highly concordant results.[14,15] The choice between MFC and RQ PCR techniques depends on the availability and level of expertise of different laboratories.

RQ-PCR examines unique sequences of the junctional regions of rearranged *IG*, or *TCR* genes for which allele-specific oligonucleotides (ASO) are developed for each patient in Ph-negative B-cell ALL and T-cell ALL.[14,16] Primers identified at baseline are then used for MRD quantification in subsequent post-therapy samples. Despite having a greater sensitivity than MFC (down to 10^{-5}), designing ASO-PCR for each patient is a time-consuming, expensive, and complicated process that requires significant expertise.[17] This method can be used in most patients with Philadelphia negative ALL.[17] However, using ASO-PCR in early precursor T-ALL is challenging because the lymphoblasts are immature and usually have not completed *TCR* gene rearrangement.[18]

Reverse transcriptase PCR (RT-PCR) is a method that utilizes the *BCR-ABL1* gene as PCR target in Philadelphia positive ALL. MRD is followed by quantifying BCR-ABL1 mRNA transcripts using the standard probes used for diagnostic.[19] This is a simple, rapid, and broadly applicable MRD detection technique in Philadelphia positive ALL.

Next-Generation Sequencing

NGS is a novel technique for detecting MRD in ALL that can address some of the limitations of traditional MRD methods. NGS use multiplex PCR without patient-specific probes to amplify various combinations of altered *IG* and *TCR* genes concurrently. Therefore, it can detect and quantify numerous clones and subclones that can be monitored during the course of treatment.[20,21] NGS is a relatively quick and reliable technique, with excellent concordance to traditional MFC or PCR procedures. An important advantage of NGS is the high level of sensitivity detecting 1 leukemic cell in 1,000,000 nucleated cells (sensitivity of 10^{-6}).[22] However, the clinical significance of very low levels of MRD is not well established. ClonoSEQ NGS technology (Adaptive Biotechnologies) has become the first NGS MRD assay in ALL authorized by the US Food and Drug Administration (FDA).[23] Additional research examining the clinical impact of this extremely sensitive technique is eagerly awaited.

Prognostic Role of MRD in ALL

MRD information has surpassed the significance of conventional risk factors for ALL such as baseline white blood cell count, cytogenetics, and immunophenotype, and became the strongest independent prognostic factor.[3,24–31] According to a large meta-analysis performed in 13,637 patients with ALL (including all ALL subtypes), those who achieved MRD negative response by MFC had superior event-free survival (EFS) and overall survival (OS). The 10-year EFS rate for MRD negative versus MRD positive patients was 77% vs 32% in children and 64% vs 21% in adults.[32] A subsequent meta-analysis performed in adult patients with ALL confirmed these findings by demonstrating significant survival benefit for patients who achieved MRD negativity.[33] Even though each contributing study differs in its design and patient demographics, these results support the use of MRD as a clinical tool for evaluating prognosis in ALL.

Depth of MRD

Among patients with detectable MRD, the level of MRD may also have prognostic implications. In one study, ALL patients with relatively lower MRD levels (10–4/10–3 versus 10–1) by either MFC or ASO-PCR had superior relapse free survival (RFS) and OS rates.[34] Although the achievement of lower MRD levels was favorable, the best outcomes were achieved with the absence of MRD.

Time to MRD Negativity

Along with the depth of the MRD response, time to MRD negativity is a clinically significant predictor of outcome, as demonstrated in multiple studies.[25,35] For example, in a recent study, 215 patients with Philadelphia B-ALL were classified according to the length of time required to achieve MRD response (early vs late MRD negativity).[35] Patients who achieved MRD negativity early (median time to MRD negativity 24 days) had significantly superior 3-year EFS and OS as compared with late MRD responders (median time to MRD negativity 110 days), 65% and 76% vs 42% and 58%, respectively. In a study by Bruggeman et al. PCR was used to track MRD in 196 patients for up to 9 months in the first year of treatment.[27] The frequency of MRD positivity dropped from 88% at early induction to 13% at week 52.[27] Identification of MRD predicted relapse at different time periods.[27] For patients with fast MRD drop to 10^{-4} or below detection limit on days 11 and 24, the 3-year relapse rate was 0%.[27] A high-risk group of 23% had an MRD of 10^{-4} or higher until week 16, with a 3-year relapse risk of 94%.[27] These findings suggest that the impact of early MRD eradication is important and should be evaluated prospectively in future clinical trials in ALL.

Impact of Baseline Genomic Aberrations

Concurrent use of MRD information and baseline cytogenetic and molecular abnormalities in different ALL subtypes may enhance prediction of relapse. In one study, detection of *IKZF1* gene deletion and *MLL* gene rearrangement in B-ALL, absence of *NOTCH1/FBXW7* mutation and presence of *KRAS/NRAS* mutation or *PTEN* alterations in T-ALL were associated with poor outcomes.[28] Both detectable MRD and unfavorable molecular alterations were independently associated with relapse and poor OS. In another study, baseline cytogenetic abnormalities such as low hypodiploidy/near triploidy and complex karyotype (defined as ≥5 chromosomal abnormalities) were associated with worse outcomes irrespective of MRD status.[36] Hence, while achievement of undetectable MRD is a desirable outcome for all patients, it may not overcome the unfavorable impact of high-risk cytogenetic and molecular alterations. Prospective clinical trials are required to determine how to incorporate MRD status, cytogenetic, and molecular profiling into risk stratification schemes.[37]

Philadelphia-Chromosome Positive ALL

The presence of *BCR/ABL1* fusion gene product provides an additional MRD monitoring tool for patients with Philadelphia positive ALL. Detection of MRD by RT-PCR of BCR/ABL1 transcripts is associated with worse outcomes.[31,38,39] In a study, 85 patients with newly diagnosed Philadelphia positive ALL who received hyper-CVAD plus a tyrosine kinase inhibitor had MRD assessments at remission (CR) and at a 3-month time point.[40] Achievement of complete molecular remission (undetectable BCR ABL 1 transcript by PCR) at the 3-month mark was significantly associated with longer OS (median 127 versus 38 months). Prospective clinical trials incorporating MRD-based treatment strategies for patients with Philadelphia positive ALL may elucidate the ideal post-remission therapy.

The Impact of Peritransplant MRD

Identification of MRD in both pre-and-post-ASCT settings predicts worse outcomes.[41,42] In a study, adult ALL patients with pre-ASCT MRD a level $\geq 10^{-4}$ (measured by NGS) were more likely to relapse after ASCT (HR 7.7, 95% CI: 2.0–30, $p < 0.01$).[43] Similarly, in pediatric patients, achieving MRD negativity prior to ASCT resulted in significantly better DFS and OS than those with positive MRD; 83% and 92% vs 41% and 64%, respectively.[42] In a prospective study of pediatric patients with R/R ALL, pre-ASCT MRD was prognostic in the setting.[41] MRD emergence after ASCT is also a sign of impending relapse. In a study of patients with ALL who were treated on Northern Italian leukemia group protocols, identification of MRD as measured by RQ-PCR at day +100 after ASCT was associated with a higher risk of relapse as compared with patients with undetectable MRD; 80% versus 7%, respectively.[44] These data suggest that sequential MRD monitoring after ASCT has crucial importance as it may guide early post-ASCT therapy.

Role of MRD in Salvage Settings

While MRD status is significantly prognostic in the frontline setting, its impact is less clear in the salvage setting. The significance of MRD status seems to be more pronounced in earlier salvages than in later salvages. In a study of 130 patients with R/R ALL, achievement of MRD negativity (by MFC) at the time of best response was shown to be associated with superior EFS; median 18 versus 7 months, in the first salvage setting.[45] However, achievement of MRD negative CR in the second and beyond salvages had no impact on survival. Patients who achieved undetectable MRD and underwent ASCT had the best outcome (2-year OS rate of 65%), irrespective of salvage status.

Role of MRD in Treatment Decisions

MRD status is used not only for risk stratification but also for post-induction treatment decision-making. By tailoring therapy based on MRD, patients with a high probability of relapse may receive risk-adapted treatments, such as the inotuzumab ozogamicin (anti-CD22 antibody-drug conjugate) or blinatumomab (CD3-CD19 bispecific T-cell engager), with or without subsequent ASCT. On the contrary, patients with a lower possibility of relapse (early MRD negativity, absence of adverse risk cytogenetic and molecular abnormalities) may benefit from less intensive treatment approaches and potentially avoid ASCT in CR1.

Eradicating MRD with ASCT

ASCT in CR1 is associated with a lower possibility of relapse and longer OS in patients with ALL who failed to achieve MRD negative response.[46] The German multicenter study group for adult ALL (GMALL 07/03 trial) prospectively investigated the impact of MRD ($\geq 10^{-4}$ measured by RQ-PCR) after induction/consultation therapy in patients with Philadelphia negative ALL.[3] Overall, 47% of the patients with suboptimal MRD response received ASCT in CR1. Furthermore, the probability of continuous CR (after five years) was higher for patients with suboptimal MRD response and ASCT in CR1 than those without ASCT in CR1 (66% versus 12%; $P < 0.0001$). The Landmark analysis also showed superior 5-year OS for patients who received ASCT in CR1 than those who received no ASCT (54% versus 33%; $P=0.06$). Conversely, patients who achieved MRD negative status had 5-year OS rates of 81% in the absence of ASCT. In the ALL-AR-03 clinical trial (PETHEMA, Treatment of High-Risk Adult Acute Lymphoblastic Leukemia [LAL-AR /2003]), patients with high risk (age 30–60 years, MLL rearrangement, or WBC > 30×10^9/l) Philadelphia-chromosome negative ALL were assigned to chemotherapy alone or chemotherapy followed by ASCT based on MRD response and early cytologic response (less than 10% leukemic blasts in bone marrow at day 14 of induction). Patients with the optimal response (MRD by MFC $\leq 10^{-4}$ and early cytologic response) continued to receive chemotherapy alone (N=108), and others with suboptimal response were assigned to receive ASCT (N=71). The 5-year DFS and OS in patients who have achieved optimal and suboptimal responses were 55% and 59%, and 32% and 37%, respectively. Both clinical trials suggest that MRD assessment at CR can be used to select patients who are likely to benefit from ASCT in CR1. They also highlight the relatively poor outcomes for patients who undergo ASCT with persistent MRD.

Total body irradiation (TBI) based conditioning regimens are the standard of care in the treatment of patients with ALL who requires ASCT. However, TBI is associated with late side effects, and therefore regimens without TBI have also been developed. In a retrospective study, NGS-based pre-ASCT MRD assessment was performed in 56 children and young adults with ALL.[47] It was shown that patients with negative MRD by NGS before ASCT had very low risk of relapse irrespective of receiving TBI or non-TBI-based conditioning regimens. These findings suggest that TBI may be reserved for patients with positive pre-ASCT MRD.

Eradicating MRD with Therapies Other Than ASCT

Blinatumomab

Targeted therapies with alternative mechanisms of action may eradicate MRD and prevent relapse. Given its efficacy in patients with low disease burden, blinatumomab arises as a promising agent for the treatment of MRD.[48] In a single-arm Phase 2 study (BLAST), adult patients with B-cell ALL in CR with detectable MRD ($\geq 10^{-3}$ measured by RQ PCR) were treated with blinatumomab for up to 4 cycles.[49] Of the 116 patients who received blinatumomab, 78% achieved MRD

negative status after one cycle. Despite the inclusion of patients in second or later remission (35%), the median OS was 36.5 months. In a landmark analysis, complete MRD responders had significantly superior RFS (23.6 versus 5.7 months, P = 0.002) and OS (38.9 versus 12.5 months, P = 0.002) compared with MRD non-responders. Based on these results, the FDA approved blinatumomab for the treatment of B-cell ALL patients with detectable MRD.[50]

While the BLAST study was neither planned nor powered to evaluate the impact of ASCT after blinatumomab therapy, in a post-hoc analysis, investigators found no statistical difference in OS between transplanted (N=74) and non-transplanted patients (N=36) [p=0.24], in part because 27% of ASCT recipients died from ASCT-related complications. Interestingly, 33% of MRD responders did not receive any additional therapy after completing 4 cycles of blinatumomab, and 25% (9 of 36) of them remained in CR after a median 24 months of follow-up, suggesting that group of patients with positive MRD who respond to blinatumomab can achieve durable remission without the need of ASCT.

In the GMALL Trial 08/2013, 705 patients with newly diagnosed ALL (median age 35, range 18–55 years old) were treated on BFM-based pediatric inspired induction regimens.[51] Patients with high-risk features (WBC>30,000, KMT2A rearrangements, ETP-ALL, Philadelphia positive) were considered for allogenic transplant in CR1.[51] Patients with molecular failure after first cycle were candidate for targeted therapy (blinatumomab, nelarabine) followed by bone marrow transplant.[51] Investigators compared the role of allogenic transplant versus standard risk therapy in high-risk patients with molecular remission after induction.[51] Overall, molecular CR rates after cycle 1 was 61%.[51] In total, 51 patients with molecular failure became candidates for targeted therapy and evaluable for assessment.[51] The molecular response was achieved in 55% (n=40) and 18% (N=11) after 1 cycle of blinatumomab or nelarabine, respectively.[51] The 3-year overall survival rate was 72% in patients with molecular failure.[51] This large, prospective multicenter clinical trial is still ongoing.[51] Preliminary results are promising for the combination of targeted therapy and allogenic transplant for patients with molecular failure.[51]

Inotuzumab Ozogamicin

Inotuzumab, an anti-CD22 antibody conjugated to calicheamicin, is a highly efficacious antibody-drug conjugate for patients with R/R B cell ALL. In INO-VATE trial, patients with R/R ALL were randomized to receive inotuzumab versus conventional chemotherapy. The CR rate was significantly higher in the inotuzumab group than in the conventional chemotherapy group (80.7% versus 29.4%, P<0.001). Compared with blinatumomab, inotuzumab appears to be more effective in inducing CR (80.7% versus 44% comparing across randomized Phase 3 trials) in R/R setting.[52,53] However, the feasibility and role of inotuzumab in eradicating MRD are unknown. A clinical trial using inotuzumab for patients with B-cell ALL who have persistent or recurrent MRD is currently ongoing (NCT03441061).

CAR T-Cell Therapies

CD19-targeted chimeric antigen receptor (CAR) T-cell therapies are more effective in eradicating the disease in patients with low burden disease than in those with frank relapse. In a Phase 1 clinical trial, 53 patients with R/R B-cell ALL were treated with autologous CD19 CAR T-cells, and CR was observed in 83% of the patients.[54] Patients with a low disease burden (defined as <5% bone marrow blasts) at baseline had longer remission duration and survival compared with patients with a higher disease burden (median EFS 11 versus 5 months, P = 0.01; median OS 20 versus 12 months, P = 0.02, respectively). These findings highlight that CAR T-cell therapy may play an essential role in the management of MRD, where such treatment may potentially cure a subset of patients.

Eradicating MRD in the Frontline Setting

Philadelphia-Chromosome Negative ALL

Expected outcomes in older ALL patients are poor, primarily due to adverse disease features and treatment-related toxicities, including prolonged myelosuppression and infections. In a study, 122 newly diagnosed older patients (age ≥ 60 years old) with Philadelphia negative B-cell ALL were treated with intensive chemotherapy (Hyper CVAD). The induction mortality rate, the death rate in CR, and the 5-year OS rate were 10%, 34%, and 20%, respectively.[55] In the same study, 34 patients were treated with low-intensity chemotherapy (various pre-Hyper CVAD regimens). Although the death in CR rates were lower (15% versus 34%) in patients who received low-intensity chemotherapy, the risk of relapse was significantly higher (80% versus

40%). To increase efficacy and reduce toxicity in older patients with newly diagnosed Philadelphia negative B-cell ALL, a phase 2 clinical trial evaluated a combination of low-intensity chemotherapy (mini-Hyper CVD; a low-intensity version of the conventional Hyper CVAD) with inotuzumab.[56] Of the 48 patients evaluable for morphological response, 47 (98%) achieved a response with induction mortality of 0%. Overall, 47 patients had MRD assessment (measured by MFC) within 3 cycles of therapy, 45 (96%) achieved MRD negativity (at any time point). The reported 3-year OS rate was 56%, which compares favorably with historical outcomes.[57] In another phase 2 study, 29 older adults (median age 75, range 66–84) with newly diagnosed B-cell ALL were treated with blinatumomab (up to 3 cycles) and followed by 18 months of maintenance POMP therapy.[58] Overall response rate and MRD negativity in responders were 66% and 92%, respectively. In this preliminary report, the 1-year OS was reported as 65%, with no induction mortality. Given its high MRD eradication potential, blinatumomab is currently being investigated in frontline therapy of younger adults with Philadelphia negative B-cell ALL. In a phase 2 study, 34 patients with newly diagnosed Philadelphia negative B-cell ALL (median age 36, range 17–59 years old) were treated with HyperCVAD and sequential blinatumomab.[59] The CR and MRD negativity (by MFC) rates were 100% and a 97% MRD respectively.[59] The anticipated 2-year OS of 86% compared well to the historical controls.[59]

Blinatumomab and inotuzumab are highly efficacious novel agents for eradicating MRD in ALL. Innovative clinical trials exploring various dose schedules and combinations of these agents with conventional chemotherapy for younger and older patients with Philadelphia-chromosome negative B-cell ALL are ongoing (NCT01371630, NCT02877303, NCT03150693).

Philadelphia-Chromosome Positive ALL

Achievement of undetectable MRD affects outcomes favorably in patients with Philadelphia-chromosome positive ALL. Combined with intensive chemotherapy, ponatinib, a third-generation pan-BCR-ABL tyrosine kinase inhibitor, is associated with high complete molecular remission rates, resulting in superior OS compared with regimens incorporating earlier generation tyrosine kinase inhibitors such as dasatinib or imatinib. In a single-arm phase 2 study, patients with newly diagnosed Philadelphia-chromosome positive ALL were induced with Hyper CVAD + ponatinib, and all patients (100%) achieved a response with no early mortality.[60] Of the 76 patients who had RT-PCR-based MRD assessment at any time point, 63 (83%) achieved complete molecular remission. The 3-year EFS and OS rates were 70% and 76%, respectively. In a propensity score analysis comparing outcomes from two phase 2 clinical trials, Hyper CVAD + ponatinib was associated with better complete molecular response rate and OS than hyper CVAD + dasatinib.[61] All ASCT recipients for Philadelphia-positive ALL should receive post-ASCT tyrosine kinase inhibitor to reduce risk of relapse, particularly patients with detectable peritransplant MRD.[62] Blinatumomab is also effective in Philadelphia chromosome-positive ALL in both R/R settings and for MRD clearance.[49,63] In a phase two study of the combination of blinatumomab and dasatinib in adults with newly diagnosed Philadelphia chromosome positive ALL (median age 54), 98% of patients achieved complete remission, with 60% achieving molecular remission after two cycles.[64] With a median follow-up of 18 months, the median OS and DFS were 95% and 88%, respectively.[64] When blinatumomab is combined with a more potent tyrosine kinase inhibitor, such as ponatinib, even deeper molecular responses occur in a greater number of patients. In a preliminary report involving 28 patients with newly diagnosed or R/R Philadelphia chromosome positive ALL, the combination of blinatumomab and ponatinib achieved a response rate of 95%, with 86% achieving complete molecular remission.[65] Several clinical trials are therefore investigating frontline regimens with blinatumomab and tyrosine kinase inhibitor combinations with the aim of superior MRD clearance with tolerable toxicity and minimizing the need for ASCT in these patients (NCT02143414, NCT 02744768, NCT03263572).

Conclusion

MRD status provides valuable information in the management of patients with ALL. Apart from its prognostic significance, MRD status guides post-remission treatment strategies, including utilization of novel chemotherapeutics, ASCT decision, conditioning regimen selection, maintenance therapies, and predicting/treating impending relapse. The development of highly sensitive MRD assays, such as NGS and RQ PCR, may provide even better risk stratification and increase its role in treatment decisions. In addition, the availability of agents highly effective in MRD settings, including inotuzumab, blinatumomab, and CAR T-cells, made it possible to develop frontline regimens with early MRD eradication

potential. While long-term follow-up of this approach is still missing, it holds promise in minimizing the need for intensive post-remission chemotherapy, including ASCT for many patients with ALL.

Disclosure

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