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Refining post-blinatumomab risk stratification through ultrasensitive-based measurable residual disease assessment

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Short title: NGS MRD post blinatumomab

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Measurable residual disease (MRD) response is widely recognized as the most powerful prognostic indicator for survival outcomes in acute lymphoblastic leukemia (ALL).[1] MRD response plays a key role in frontline therapeutic algorithms, stratifying patients risk and determining their eligibility for transplant consolidation.[2] Beyond its prognostic value, MRD relapse or persistence in patients with B-cell ALL identifies candidates for immunotherapies such as blinatumomab,[3,4] with growing evidence supporting the use of MRD-directed chimeric-antigen receptor (CAR) T-cell therapy and inotuzumab ozogamicin.[5,6]

Blinatumomab, a CD3-CD19 bispecific T cell engager, received regulatory approval for the treatment of MRD-positive relapsed or refractory B-ALL based on the BLAST study.[3] In this trial, 116 adults with persistent marrow MRD at levels ≥0.1%, measured centrally using real-time quantitative PCR for clonally rearranged immunoglobulin and/or T-cell receptor gene sequences, or by central-lab flow cytometry, after at least three prior blocks of chemotherapy were eligible. Patients received up to four cycles of blinatumomab. Treatment was safe and highly effective, achieving MRD negativity in 78% of participants.[3]

Real-world experience has broadened the use of blinatumomab for MRD eradication to include patients with disease levels below 0.1% and demonstrated its capability to convert residual disease to MRD-negative status.[7,8] More recently, blinatumomab has also been approved as consolidation therapy for patients who achieve MRD negativity following chemotherapy defined as <0.01%, and its application in this setting improved survival outcomes in both patients with and without detectable MRD below 0.01%.[4]

Lower disease burden has long been correlated with better responses to blinatumomab in relapsed/refractory B-ALL,[9] but the BLAST study did not clearly demonstrate this relationship.[3] Given the very narrow MRD range allowed in BLAST (all patients had MRD ≥0.1% and were otherwise in hematologic remission), the study was not well positioned to distinguish outcome differences across a broader disease-burden spectrum. In contrast, real-world cohorts from France and City of Hope suggested that disease burden continues to matter even within the MRD-positive population.[7,8] Patients

with lower MRD levels at the time of blinatumomab initiation achieve higher rates of MRD clearance and improved survival outcomes compared with those who have higher MRD levels.

The BLAST study suggested that a subset of patients treated with blinatumomab for MRD-positive disease could achieve durable remissions without additional consolidation therapy.[3] This finding has generated considerable interest, particularly for older or frail patients who may not be candidates for transplant, as blinatumomab could offer a potential path to cure with relatively low toxicity. However, most patients in the BLAST study ultimately proceeded to transplant and experienced excellent outcomes. Transplant following blinatumomab was associated with a lower risk of relapse but a higher risk of non-relapse mortality. These observations highlight the need to determine which MRD-positive patients treated with blinatumomab may achieve cure without proceeding to transplant, and whether specific intrinsic leukemia features or response-related factors, such as the depth or kinetics of MRD clearance, can more accurately identify these individuals.

In the report published in this issue of *Haematologica*, Short and colleagues from MD Anderson Cancer Center present some of the first data on the efficacy of blinatumomab in eradicating low-level MRD measured by next-generation sequencing (NGS) using the clonoSEQ assay.[10] ClonoSEQ can detect MRD down to a sensitivity of 10^{-6}, surpassing all currently available MRD assays for ALL.[11] Compared with MRD assessment by flow cytometry or PCR, clonoSEQ has demonstrated superior sensitivity and specificity in both Ph-negative and Ph-positive ALL.

Among 100 patients treated with blinatumomab for MRD-positive disease in the study, only 38 had post-treatment MRD assessment performed by clonoSEQ, including 26 with Philadelphia (Ph)-negative ALL. The MRD response rate by NGS was 66% overall, with responses of 54% in Ph-negative ALL and 92% in Ph-positive ALL, the latter of whom received concurrent tyrosine kinase inhibitors (TKIs). MRD response rates were 69% for patients treated in first complete remission (CR) and 50% for those in second CR, although the sample size was limited for those treated beyond CR1. Among NGS MRD responders, the 2-year relapse-free survival (RFS) and overall survival (OS) were 73% and 91%, respectively, despite only two responders proceeding

to allogeneic hematopoietic stem cell transplant (HSCT). The benefit of achieving an MRD response was most pronounced in standard-risk Ph-negative ALL, where the 2-year RFS was 100%, compared with 51% among high-risk responders. In a landmark analysis of non-responders, allogeneic HSCT was associated with numerically superior outcomes, with a 2-year RFS of 71% versus 27%.[10]

The retrospective design, small sample size, and heterogeneity of the study population- including differences in disease subtype, prior therapy exposure, and lack of standardized approaches to allogeneic HSCT consolidation—pose significant challenges to interpreting the findings and drawing firm conclusions. Despite these limitations, the results suggest that clonoSEQ may enhance our ability to identify patients who could potentially be cured with blinatumomab as a standalone therapy for MRD-positive disease, allowing some individuals to safely defer transplant until possible relapse. Patients with standard-risk Ph-negative ALL appeared to have particularly favorable outcomes, with no relapses or events observed at 2 years; however, this observation is based on only seven patients and should be interpreted with extreme caution. In contrast, patients with high-risk cytogenetic or molecular features—who also constitute most individuals with persistent MRD following chemotherapy—may not achieve sufficient disease control with blinatumomab alone. For these patients, consolidation with allogeneic HSCT remains the recommended approach.

Although allogeneic transplant appears to provide benefit for clonoSEQ non-responders, prior studies have consistently shown that proceeding to transplant with detectable MRD is associated with a higher risk of relapse,[12] and therefore optimizing MRD status before transplant remains strongly recommended when feasible. However, recommending additional immunotherapy for patients with very low-level NGS- or PCR-positive MRD—below the threshold detectable by flow cytometry—after blinatumomab presents several challenges. These include uncertainty regarding continued CD19 expression after prior CD19-directed therapy and the unclear efficacy of further immunotherapy in this setting, particularly if such treatment delays a potentially beneficial transplant.

This study contributes to the growing body of evidence suggesting that deeper MRD clearance correlates with improved clinical outcomes and suggests that a subset

of patients who achieve NGS-negative remission, particularly standard risk ALL, may not require allogeneic HSCT for consolidation. Nonetheless, larger, well-designed, and ideally prospective studies are needed to more definitively address this question, particularly in the evolving therapeutic landscape marked by expanding access to chimeric antigen receptor T-cell therapies and the emergence of newer, highly active CD19-targeted bispecific antibodies.

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