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CLINICAL TRIALS AND OBSERVATIONS

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Blinatumomab for MRD$^+$ B-ALL: the evidence strengthens

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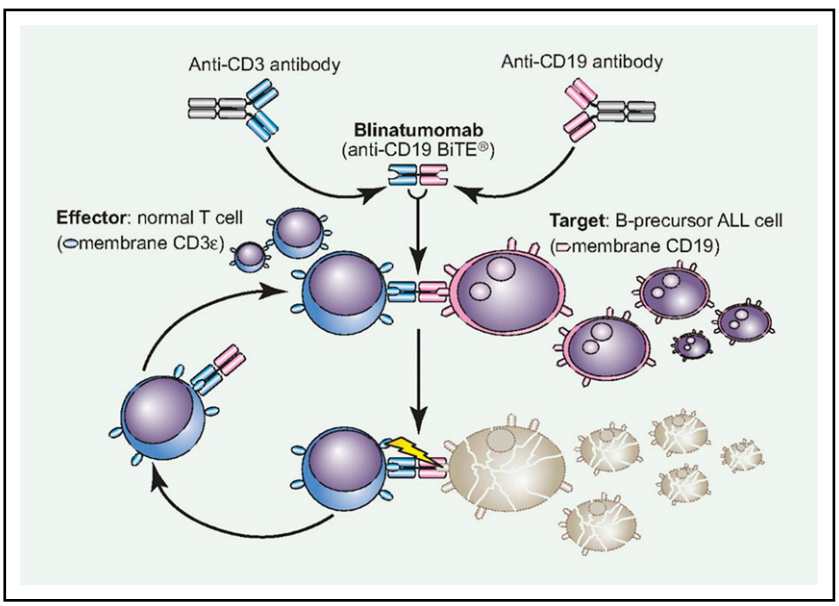
In this issue of *Blood*, Gökbuget et al provide strong evidence that immunotherapy with blinatumomab can eliminate residual chemotherapy-resistant B-cell acute lymphoblastic leukemia (B-ALL) cells and that this prevents subsequent relapse and improves survival.[1] This addresses the most important unsolved clinical problem in adults with B-ALL: the development of chemotherapy-resistant relapsed disease.

The strongest independent predictor of outcome in B-ALL, in both children and adults, is the persistence of minimal residual disease (MRD) in the bone marrow despite 1 or more courses of intensive multiagent chemotherapy.[2,3] MRD assays can detect leukemia down to levels of 1 in 10 000 cells (10^{-4} or 0.01%). Approximately 30% to 50% of adults remain MRD-positive (MRD$^+$) after chemotherapy despite having no leukemia detectable by microscopy, and these patients have a three- to fourfold higher risk of subsequent relapse and death.[4,5] Allogeneic hematopoietic stem cell transplantation (HSCT) improves outcomes among MRD$^+$ adults, but many patients cannot undergo HSCT because of early relapse or comorbidities, and persistent MRD at the time of HSCT is associated with higher subsequent relapse rates.[5]



Blinatumomab is a bispecific construct that reacts simultaneously to normal CD3$^+$ T cells and CD19$^+$ ALL cells, creating a tight intercellular connection followed by T-cell–mediated cytotoxicity exerted on CD19$^+$ blast cells (bispecific T-cell engaging [BiTE] mechanism).[9] Professional illustration by Paulette Dennis.

Because MRD is the result of persistence of B-ALL cells despite multiagent chemotherapy, immunotherapy may circumvent chemotherapy resistance and eliminate MRD. The recent approval by the US Food and Drug Administration (FDA) of 3 different immunotherapies (blinatumomab,[6] inotuzumab,[7] and tisagenlecleucel[8]) for inducing remission in refractory or relapsed B-ALL has intensified interest in these strategies for preventing relapse in MRD$^+$ patients, especially since all 3 treatments are most effective for patients with relatively low burdens of disease at the time of treatment.

Blinatumomab, a bispecific T-cell engaging antibody that directs cytotoxic T cells to CD19$^+$ cells (see figure[9]), is the first of the immunotherapies to be studied in MRD$^+$ adult B-ALL. The results are indeed quite promising, but they also leave a number of questions to be answered.

The trial reported here was a well-designed and well-executed international, multicenter, single-arm phase 2 study that treated 116 patients and observed them for clearance of MRD (primary end point), relapse, and survival. This was a logical extension of a previous small pilot trial of 20 patients in first remission with MRD $>10^{-4}$ that reported clearance of MRD in 16 patients (80%)[10] and an impressive relapse-free survival (RFS) in 12 patients (60%) with almost 3 years of follow-up.[11] Perhaps most intriguing was the fact that of the 12 patients who remained in prolonged remission, 6 had not received HSCT after blinatumomab. Notably, the patients in the follow-up trial reported here represent a substantially higher risk group than patients in the pilot trial, in that the threshold for MRD

positivity was 1-log higher (>10^{-3}), and 35% of the patients had already relapsed at least once and were MRD$^+$ after salvage re-induction chemotherapy. Despite this, the results are remarkably comparable to those of the pilot study. MRD clearance rate was 78% after one 28-day cycle of blinatumomab, and RFS was 54% with a median follow-up of 30 months. Adverse events were modest. Although neurologic adverse events were seen in 10% to 15% of patients, these were reversible with interruption of the infusion and with supportive care. Cytokine release syndrome, which has been a significant limitation in studies of both blinatumomab and tisagenlecleucel in the relapsed/refractory setting, was comparably mild in the MRD$^+$ setting.

One crucial question this study seems to answer is whether persistent MRD is a modifiable risk factor in B-ALL. In other words, does immunotherapeutic elimination of MRD actually translate into better outcomes? The answer is yes. Overall survival (OS) was doubled and RFS was tripled in MRD responders vs nonresponders. An important caveat, however, is that although the MRD clearance rate was no lower in the 35% of patients who had already relapsed once before enrolling, these patients had a substantially inferior RFS and OS compared with those treated in first remission. The clear lesson is that the impact of immunotherapeutic clearance of MRD on survival is greatest when applied early in the disease course.

The most pressing question left unanswered by this study is the role of HSCT after immunotherapeutic clearance of persistent MRD in B-ALL. In both the pilot study and this study, HSCT was optional. Understandably, the previous studies that demonstrated superior outcomes for MRD$^+$ patients receiving HSCT led to 67% of patients on this study proceeding to HSCT. In both the pilot study and this study, a significant number of patients who received no additional treatment after clearance of MRD with blinatumomab remain in prolonged remission. Conversely, 20 (27%) of 74 patients proceeding to HSCT died as a result of transplant-related mortality. Because this study was not designed or powered to answer whether HSCT does or does not improve outcomes in MRD$^+$ patients after immunotherapeutic clearance of MRD, further study will be needed.

There are other intriguing questions yet to be answered. Blinatumomab efficacy relies upon a functional endogenous cytotoxic T-cell response, and resistance seems to be related primarily to T-cell exhaustion. Would combining blinatumomab with checkpoint inhibitors further enhance efficacy? Another mechanism of resistance to blinatumomab (and other CD19-targeted immunotherapies, such as the chimeric antigen receptor T-cell product tisagenlecleucel) is the emergence of CD19$^-$ subclones. Unfortunately, this report does not address the CD19 status of relapses, but to the extent that this is an issue, would multi-antigen targeting (combined CD19 and CD22, for example) prevent antigen escape? Finally, how would the other 2 FDA-approved immunotherapies (inotuzumab ozogamicin, a CD22-directed immunotoxin, and tisagenlecleucel) compare with blinatumomab when used in the MRD$^+$ setting?

Further studies will be needed, and many of these are already underway. It is indeed an exciting time for B-ALL patients and their providers. It is tantalizing to imagine that with optimization of immunotherapy, even the highest risk subsets of B-ALL as defined in the era of chemotherapy may prove curable.

Conflict-of-interest disclosure: The author declares no competing financial interests. ■

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