Blood Spotlight

Taking a "BiTE out of ALL": blinatumomab approval for MRD-positive ALL

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Blinatumomab, a bispecific T-cell engager (BiTE) associated with improved survival in relapsed or refractory acute lymphoblastic leukemia (ALL), was recently approved for treatment of minimal residual disease (MRD). MRD is an important predictor of survival in ALL, and recent studies suggest that achievement of MRD-negativity with blinatumomab improves outcomes in patients with ALL. However, further research is needed to determine how to optimally incorporate blinatumomab, and other novel therapies, into current therapies for ALL. (*Blood*. 2019;133(16):1715-1719)

Introduction

The recent Food and Drug Administration (FDA) approval in March 2018 of blinatumomab for patients with acute lymphoblastic leukemia (ALL) and detectable minimal (or measurable) residual disease (MRD) sets an exciting precedent for approval of new therapies for patients with hematological malignancies. To place this novel indication in context and understand how similar approaches may be applied to other treatments and diseases, it is important to evaluate the current landscape of MRD-based prognostication and treatment of patients with ALL. Exploration of approaches to optimally enhance our treatment strategies, such as by employing active new immune targeting into frontline therapy, may facilitate the eradication of MRD to further improve survival rates.

Blinatumomab clinical trials

Relapsed/refractory ALL

Blinatumomab is a bispecific T-cell engager (BiTE) targeted to CD19 and CD3, which promotes immune-mediated elimination of B-cell lymphoblasts by cytotoxic T cells.[1,2] Because of the short half-life, it is administered as a continuous infusion, typically over 4 weeks with a 2-week rest period between cycles. Blinatumomab was initially FDA approved in 2014 for treatment of Philadelphia chromosome (Ph)–negative relapsed or refractory B-cell acute lymphoblastic leukemia (B-ALL), based on the pivotal phase 2 trial by Topp and colleagues that demonstrated a complete remission (CR) rate of 43% in this patient population, with (CR) or without hematologic recovery (CRh).[3] The majority of patients who achieved CR/CRh did so within the first cycle (78%), and 82% of these patients had an MRD response, defined as $<10^{-4}$ detectable blasts.

Further follow-up in a multicenter randomized phase 3 trial demonstrated significantly longer overall (OS) survival in patients treated with single-agent blinatumomab than among those treated with standard-of-care chemotherapy (7.7 months vs 4.0 months, $P = .01$).[4] Remission rates were similar to the phase 2 trial, with CR/CRh of 43.9% within the first 2 cycles. As in the phase 2 trial, the majority of responders (76%) achieved MRD negativity, and a lower percentage of baseline bone marrow blasts was associated with increased CR/CRh (65% vs 34.4% for bone marrow blasts <50% or ≥50%, respectively). Subsequent trials in Ph^+ and pediatric ALL demonstrated CR/CRh rates of 36% and 39%, respectively,[5,6] leading to expansion of FDA approval for these indications in July 2017.

MRD^+ ALL

It has become increasingly clear that early achievement of an MRD-negative marrow is a critical and, perhaps, the most powerful prognosticator of event-free survival for all subsets of ALL.[7-9] In a large meta-analysis, achievement of MRD negativity was significantly associated with improved event-free survival in both children and adults (hazard ratio [HR] 0.23 and 0.28, respectively).[10] An early phase 2 trial by Topp and colleagues investigated the use of blinatumomab to eradicate MRD in patients with B-ALL in first remission and demonstrated an 80% MRD response rate.[11] All of the MRD responses, defined as 10^{-4} or less, occurred at the end of the first cycle, and, at a median follow-up of 33 months, recurrence-free survival (RFS) was 61%, including 6 of 11 patients (60% RFS) who had not received hematopoietic stem cell transplant (HSCT).[12]

These results prompted a larger phase 2 trial by Gökbuget and colleagues, in which 116 adult patients with ALL in first or later CR and MRD $\geq 10^{-3}$ after at least 3 blocks of chemotherapy were treated with blinatumomab for up to 4 cycles.[13] Results were similar to the earlier trial, with the vast majority (88%) of patients achieving an MRD response, and with 18-month RFS and OS of 53% and 67%, respectively. MRD responders had significantly improved RFS and OS, compared with MRD nonresponders (median RFS 23.6 vs 5.7 months, median OS 38.9 months vs 12.5 months). Based on these findings, in the spring of 2018, blinatumomab became the first FDA-approved treatment for patients with MRD-positive ALL and achieved the distinction of

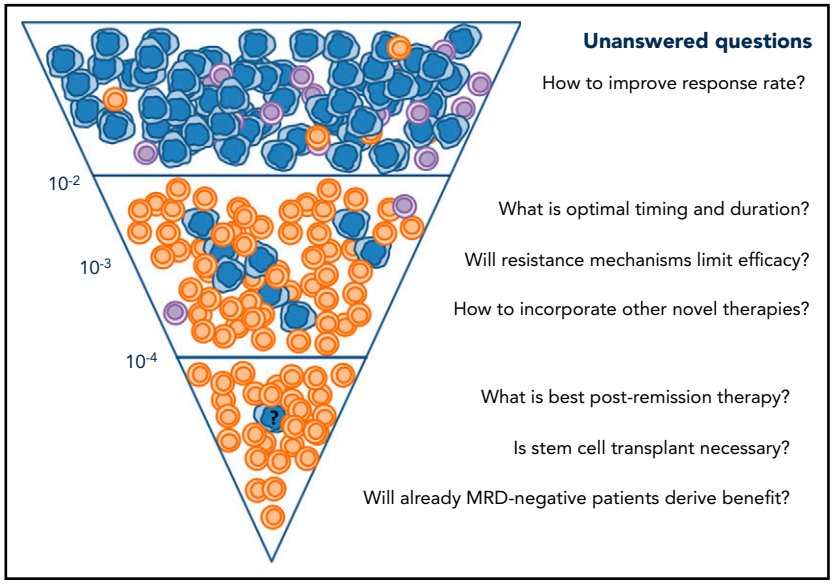

Figure 1. Challenges of blinatumomab for MRD in ALL. Decreasing levels of MRD with increasing ratio of effector T cells (orange) to leukemia cells (blue). Regulatory T cells are indicated in purple.

becoming the first drug approval in ALL based on an MRD endpoint. Outcomes from a longer median follow-up of >4 years demonstrate a median OS of 36.5 months, thus confirming and extending these observations.[14]

Incorporating blinatumomab into frontline therapy

The addition of other antibody therapies, such as rituximab, significantly improves survival when combined with chemotherapy in the frontline setting.[15,16] Whether the combination of blinatumomab with standard frontline chemotherapy therapy will also improve survival is still an ongoing area of investigation, but the initial results are encouraging. Results from randomized trials, such as the ongoing US intergroup study, E1910 (#NCT02003222), will more definitively address this issue. However, many questions remain regarding how and when blinatumomab and/or other active new immune targeted therapies should be incorporated into frontline treatment of ALL, as well as the role of allogeneic stem cell transplant.

MRD assessment

Several methods exist to measure MRD, with the most widely used being multiparametric flow cytometry (in North America) to identify cells with a leukemia-specific immunophenotype and reverse transcription quantitative polymerase chain reaction (in Europe) to detect immunoglobulin and T-cell receptor gene rearrangements. In general, reverse transcription quantitative polymerase chain reaction is a log-fold more sensitive in detection of MRD than flow cytometry (10^{-5} vs 10^{-4}), but is limited by more time-intensive techniques and the fact that specific clones are unable to be identified in a small subset of patients.[17] Novel methods of measuring MRD, using next-generation sequencing and improved flow cytometry, appear to increase the sensitivity of detection of MRD even further; thus, improved MRD detection methods may further refine our ability to evaluate the impact of specific treatment modalities and guide therapeutic targeting.

Blinatumomab is currently FDA approved for patients with MRD of 10^{-3} or greater in first or second CR, based on the larger phase 2 trial by Gökbuget and colleagues,[13] although a lower cutoff of 10^{-4} was used in the earlier trial by Topp et al.[11,12] As MRD testing using next-generation sequencing platforms is increasing sensitivity of detection,[18] we are now able to identify minor clones that can give rise to relapse; whether treatment of patients with very low level MRD, or even without detectable MRD, will have a survival benefit from blinatumomab remains an open question that will also be answered, in part, by ongoing trials (such as #NCT02003222, #NCT02877303, #NCT03367299, #NCT03541083, #NCT03709719).

Timing and duration of blinatumomab

Optimal timing for an MRD-based intervention requires additional study. In the previously published trials, patients received blinatumomab if they had evidence of MRD positivity after consolidation I[11,12] or after 3 cycles of intensive multiagent chemotherapy.[13] Most studies have demonstrated that early achievement of MRD negativity is more predictive of outcome than achievement of MRD negativity later in treatment, likely due to the emergence of chemotherapy-resistant subclones.[17,19] Therefore, early introduction of blinatumomab to induce MRD negativity as early as possible may be beneficial. This concept must be balanced with the observation that blinatumomab has higher response rates for patients with lower disease burden,[3,4] and it may be important to achieve at least some degree of cytoreduction prior to introduction of blinatumomab. For instance, the ongoing SWOG 1318 trial, in which 29 older patients >65 years of age with newly diagnosed ALL were treated with single-agent blinatumomab, demonstrated an overall response rate of 66%.[20] Although these outcomes are superior to the response rate in the relapsed setting, they remain inferior to the MRD setting, suggesting that some cytoreduction may be beneficial.

Blinatumomab efficacy relies on T-cell activity, and concurrent ALL cytotoxic chemotherapy,[21] that depletes or induces dysfunction of T cells, may reduce its efficacy. Most previously published and ongoing frontline trials with blinatumomab

employ it as a single agent, sandwiched between cycles of chemotherapy.[11-13] Ongoing trials will help to determine whether it will be efficacious (or antagonistic) to combine blinatumomab during cycles of immunosuppressive chemotherapy, as in other ALL trials where rituximab has been added.[15,16]

The optimal number of cycles of blinatumomab in the setting of MRD remains an open question. The majority of patients treated with blinatumomab achieve MRD negativity within the first 1 to 2 cycles of treatment and may be sufficient to improve outcomes.[3,4,11-13] However, continuing treatment with blinatumomab could potentially induce deeper remissions that are not detectable with our current flow cytometric or polymerase chain reaction methods of MRD measurement. The majority of ongoing trials include 4 to 8 cycles of blinatumomab,[20,22,23] but further evaluation is needed to determine whether additional cycles will actually further improve disease-free survival. In addition, any negative impact of prolonged B-cell depletion on the risk of infectious complications with multiple cycles must be considered.

The important question of how to optimally deliver central nervous system (CNS) prophylaxis during treatment with blinatumomab must be addressed. Neurologic toxicities are a relatively common toxicity, with 53% of patients experiencing a neurologic adverse event, with 13% grade 3 to 4.[13] Thus, there has been justified concern regarding the safety of administering intrathecal (IT) chemotherapy concurrently with blinatumomab. Some trials administer IT chemotherapy between cycles of blinatumomab,[13,20] whereas others avoid IT chemotherapy entirely during treatment cycles.[13,20,22,23] Because there is no evidence that blinatumomab crosses the blood-brain barrier or can treat CNS disease, it will be important to carefully evaluate rates of isolated CNS or other extramedullary relapse with different treatment schedules. Interestingly, in the trial of pediatric patients with relapsed/refractory ALL leading to FDA approval, CNS prophylaxis was administered concurrently with blinatumomab without additional CNS toxicity, suggesting it is feasible and tolerated.[6] Further investigations will need to focus on determining whether IT chemotherapy can be safely administered concurrently with blinatumomab in other patient populations.

Role of transplant after achievement of MRD negativity with blinatumomab

Although still debated, it is generally accepted that ALL patients with persistent MRD benefit from HSCT. In a retrospective analysis of 522 patients aged 15 to 55 treated on Group for Research on Adult Acute Lymphoblastic Leukemia (GRAALL) regimens, HSCT was associated with significantly longer RFS (HR 0.4, $P = .001$) and OS (HR 0.41, $P = .002$) for patients with postinduction MRD of 10^{-3} or greater.[24] Interestingly, although some studies have suggested that patients who are MRD negative have superior outcomes with HSCT than MRD-positive patients,[25] on this trial, there was no significant benefit in RFS (HR 1.37, $P = .24$) or OS (HR 1.47, $P = .16$) for HSCT among patients with $<10^{-3}$ MRD.[24] If patients are able to achieve MRD negativity, it is possible that HSCT will not be needed.

Whether previously MRD-positive patients who become MRD negative with blinatumomab should then proceed to HSCT is even less clear. A large percentage (45% to 65%) of patients in prior studies of blinatumomab in the setting of MRD positivity did proceed to HSCT.[11,13] Of 11 patients in the initial study of Topp et al who had not received HSCT, 6 (60% RFS) remained in continued CR at a median follow-up of 31 months.[12] Similarly, in the larger phase 2 trial, 12 of 36 patients (33.3%) without HSCT were alive in CCR, compared with the 30 of 74 (40.5%) patients who received HSCT.[14] So, it is possible that, in patients who become MRD negative, HSCT will not be needed. The transplant-related mortality in this trial was quite high (35%), suggesting that, in many patients, the risks of transplant may outweigh the benefits following blinatumomab.[14,26] The currently published trials are not adequately powered or designed to answer this question, nor have they addressed the issue of whether and what kind of additional post–blinatumomab therapy is needed for those patients who are not transplanted after achieving an MRD-negative state.

Other remaining questions

There are many interesting and important questions that must be addressed to optimize the use of blinatumomab for treatment of MRD (Figure 1).

Mechanisms of resistance to blinatumomab

The initial trials in relapsed and refractory ALL demonstrated a CR rate of ~43%.[3,4] Although response rates were clearly higher in patients with lower disease burden,[13] alternative mechanisms of resistance to blinatumomab have been described. CD19-targeted treatment of *MLL* (*KMT2A*) -rearranged B-ALL has been reported to induce lineage switch to acute myeloid leukemia.[27-29] CD19-negative relapses, as described with chimeric antigen receptor T-cell therapy,[30] have also been reported, but this seems to be an uncommon mechanism of blinatumomab resistance.[31,32] Nevertheless, as blinatumomab use increases, CD19 target loss may become a more commonly reported event.

Because of its reliance on T-cell–mediated clearance of leukemic blasts, immune evasion pathways have been explored as another mechanism of blinatumomab resistance. Expression of T-cell exhaustion markers, such as PD-1 and PD-L1, are increased in patients with ALL, particularly in relapsed disease, and can be increased further with blinatumomab treatment.[33,34] Preclinical work suggests that PD-1 inhibition may synergize with blinatumomab,[35] and ongoing clinical trials are investigating combining the PD-1 inhibitor nivolumab and CTLA-4 blockade with blinatumomab in patients with relapsed/refractor ALL (#NCT02879695).[36] Other preclinical work suggests that higher levels of regulatory T cells dampen responses to blinatumomab,[37] and strategies to deplete regulatory T cells in combination with blinatumomab may be warranted. As new immunotherapies are developed, understanding the immune environment of ALL and role in blinatumomab response will be needed to identify which combination strategies may be most beneficial.

Extramedullary disease relapse, particularly in immune privileged sites and including but not limited to CNS disease, has been reported following blinatumomab treatment.[38,39] In some cases, these relapses occurred in the absence of morphologic disease and even in the setting of bone marrow MRD negativity,[38,39] raising concerns about the potential for an increase in nonmarrow relapse following single-agent blinatumomab

treatment. This highlights the need for a combination approach, using therapies with nonoverlapping distributions, to mitigate this potential mechanism of resistance.

The future: combined immune targeting for ALL, moving away from traditional chemotherapy

Other antibodies and immunotherapies, such as inotuzumab ozogamicin, which targets CD22 with an immunotoxin, calecheamycin, and CD19-targeted chimeric antigen receptor T cells, are very effective in relapsed/refractory ALL with even higher response rates reported than blinatumomab.[40,41] These strategies may be as effective as blinatumomab in the MRD setting, and trials are in design or underway to test these agents in this setting (#NCT03150693). Trials are ongoing that are beginning to test minimal use of traditional chemotherapy; S1318 (#NCT02143414) has reported preliminary results of single-agent blinatumomab induction/consolidation, and A041701 (#NCT03739814) tests the use of sequential inotuzumab followed by blinatumomab in frontline treatment of older patients with ALL.

Conclusions

Approval of blinatumomab for treatment of MRD$^+$ ALL is the first time in which an MRD endpoint was the basis for FDA approval of a therapeutic agent and provides a tantalizing new "weapon" for eradication of this challenging and heterogeneous group of diseases that fall under the B-ALL umbrella. The rapid approval based on nonrandomized phase 2 data, however, also raises many important questions that will need to be addressed in ongoing and future prospective trials. Thoughtful correlative studies are also required to optimize its use and facilitate design of combination immune targeting strategies in ALL. As MRD detection methods improve, these datasets will evolve and will constantly need to be reevaluated as we strive to learn how combined immune targeting can enhance survival (and potentially reduce toxicity) for our patients.

Authorship

Contribution: E.C. and W.S. designed, wrote, and edited the manuscript.

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Footnote

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