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COMMENTARY

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Inclusion of BiTEs as consolidation for MRD-negative ALL: Where are we now and where can we go?

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Bispecific T cell engagers (BiTEs) are one type of T cell-redirecting bispecific antibodies (BsAbs), which are engineered to bind to CD3 in the T cell receptor complex on one arm and antigens associated with tumor cells on the other. This design facilitates the proximity of T cells to tumor cells, enabling the formation of immune synapses. Following synapse formation, T cells are activated and release granzymes and perforins, which lead to the lysis of tumor cells. BiTE therapy offers several advantages over chimeric antigen receptor (CAR) T-cell therapy during consolidation treatment. For example, BITE therapy does not rely on the quantity or specificity of the patient's own T cells, allowing for broader applicability in treatment. This approach is particularly beneficial for patients with rapidly progressing diseases. Additionally, compared to CAR-T therapies, BiTE offers greater flexibility in dosing and administration. Furthermore, the risk of severe cytokine release syndrome (CRS) and neurotoxicity is lower with BiTE therapy, making it a more suitable option for patients with high tumor burdens or the elderly individuals.

Blinatumomab, which is composed of two single-stranded variable segments (scFv) linked by short peptides, is one of the most typical BiTEs. These two domains are designed to bind specifically to CD3 of T cells and CD19 of B cells, respectively. Given the prevalent expression of CD19 on B-cell acute lymphoblastic leukemia (ALL), blinatumomab is gaining significance as an effective therapy for these patients. The Food and Drug Administration (FDA) approved the usage of blinatumomab for the treatment of patients with Philadelphia chromosome (Ph)-negative relapsed or refractory ALL (R/R ALL) in 2014 and subsequently broadened the indications in 2018 to include B-ALL patients in their first or second CR with MRD levels of 0.1% or higher. Several single-arm clinical trials (e.g., GIMEMA LAL2317, GRAALL-2014/B study, HOVON-146, among others) have explored the induction of blinatumomab in the consolidation treatment as a replacement for select chemotherapy cycles for Ph-negative B-ALL patients. Eventually, a randomized controlled trial conducted by Litzow et al. has contributed to the expanded approval of blinatumomab for the treatment of adult and pediatric patients one month and older with CD19-positive Ph-negative B-ALL in the consolidation phase of multiphase chemotherapy in June 2024 (Figure 1).[1]

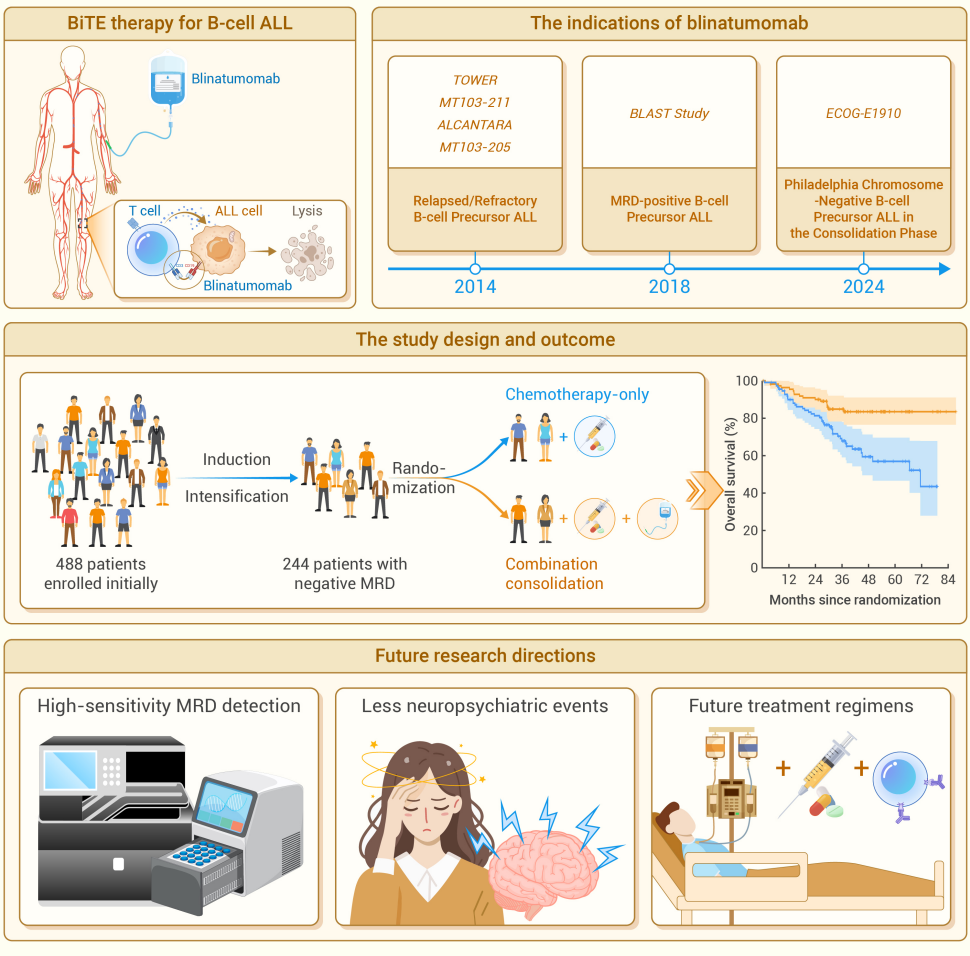

Figure 1. The development of BiTE treatment for ALL Blinatumomab can redirect T cells and B-ALL cells, activating T cells to release cytolytic proteins which lyse tumor cells ultimately. This property has made BiTE therapy a front-line regimen throughout the treatment process of B-cell ALL. BiTE=bispecific T cell engager. MRD=minimal residual disease. MT103-211: NCT01466179. ALCANTARA: NCT02000427. MT103-205: NCT01471782. BLAST study: NCT01207388. ECOG-E1910: NCT02003222.

In Litzow et al. 's phase 3 clinical trial (E1910 trial) involving 488 patients aged 30-70 years, 224 MRD-negative patients and 44 MRD-positive patients were randomly assigned to two groups: one receiving a combination of blinatumomab and chemotherapy during consolidation, and the other receiving chemotherapy alone. Upon the trial's completion, the blinatumomab arm demonstrated a substantial improvement in overall survival and 3-year relapse-free survival compared to the chemotherapy arm. Patients under the age of 55 seemed to have the greatest benefit. Nevertheless, the incidence of treatment-

induced adverse events in the blinatumomab arm was higher compared to the chemotherapy arm, with a particularly notable prevalence of neurological or psychiatric problems. This study has shown the significant efficacy of incorporating blinatumomab into consolidation chemotherapy, potentially in lowering the toxicity of chemotherapy or maintaining a more stable and deeper negative MRD which is beneficial for long-term survival. Concurrently, there are several studies (such as SWOG1318, ALLG ALL08, Alliance A041703, and others) focusing on the incorporation of blinatumomab into the consolidation therapy for elderly and frail patients who are often treated with palliative regimens and inspiring outcomes have been reported. These findings imply that blinatumomab is now an essential component throughout the treatment process of B-cell ALL, offering a strategy to decrease the intensity of chemotherapy and to serve as a replacement or partial substitute for chemotherapy.

While Litzow et al. 's study successfully expanded the usage of blinatumomab in treating MRD-negative ALL, further research is required to address several limitations in this trial. First, only 58% of the patients who originally enrolled in the study were randomly assigned, as 57% of the patients were deemed high-risk based on genomic analysis. Consequently, a bias in the results may have arisen from certain patients' inability to achieve CR to participate in the randomization. This suggests that early administration of BiTEs during induction may be beneficial for high-risk patients. Although the study demonstrated that the combination of BiTEs and chemotherapy yielded a superior survival outcome compared to chemotherapy alone as the consolidation treatment for patients with MRD less than 0.01% as detected by flow cytometry (FCM). It is evident that there are certain patients with an extremely low level (below $<10^{-6}$) of MRD that cannot be detected by FCM. Further investigation is essential to ascertain whether patients with deeply negative MRD truly derive benefit from BiTEs consolidation. This requires the employment of sophisticated detection methods to pinpoint the presence of CD19-positive leukemia cells, including next-generation sequencing (NGS) based on IGH and IGK/IGL rearrangements, as well as real-time quantitative PCR (RQ-PCR). Besides, no significant difference was observed in the percentage of patients undergoing hematopoietic stem cell transplantation (HSCT) between the two groups. A potential investigation might be conducted to assess the impact of incorporating blinatumomab into the consolidation treatment phase on the survival outcomes of patients who underwent transplantation. Simultaneously, further analysis is also required to determine if there is a survival difference between patients who proceed to HSCT and those who do not following blinatumomab consolidation. Larger-scale clinical trials are required to investigate whether adding blinatumomab to different stages of treatment for B-cell ALL can increase the likelihood of patients avoiding HSCT and whether blinatumomab can lower MRD levels more quickly, more thoroughly, and for a longer period. The possibility of HSCT-free regimens in the blinatumomab era is worth exploring.

Inevitably, there are shortcomings of blinatumomab for clinical use. Firstly, blinatumomab requires continuous administration for maximum effectiveness due to its shorter half-life compared to CAR-T cells. Additionally, a history of extramedullary disease (central nervous system involvement particularly) correlates with an inferior response to blinatumomab, predicting a higher risk of relapse.[2] As demonstrated in the study by Litzow et al., patients in the blinatumomab arm experienced a higher incidence of neuropsychiatric events compared to those receiving chemotherapy alone. This phenomenon may be attributed to an excessive immune response leading to an inflammatory reaction, manifested as CRS. Other potential contributing factors include the frequent administration or the enhanced toxicity of chemotherapy agents used in combination with blinatumomab. Furthermore, resistance is also difficult to avoid. Elevated expression of PD-L1 in ALL blast cells and increased expression of PD-1 on the surface of T cells were seen in patients with relapsed and blinatumomab-resistant ALL suggesting that ALL cells actively diminish the anti-leukemia effect of T cells by producing co-signaling molecules.[3] Tumor cell immune escape can be caused by down-regulation or deletion of the target antigen. An understanding of the mechanism behind the loss of CD19 expression might improve the prognosis of patients.

Nowadays, the pursuit of a more long-term objective involves integrating molecular-targeted therapy with immunological therapy, alongside sensitive MRD detection methods, to provide patients with a precise treatment regimen that ideally obviates the necessity for HSCT. In a study that included 63 patients with Ph-positive ALL, the 18-month OS rate was 95%, and the disease-free survival rate was 88% after induction and consolidation therapy with dasatinib and blinatumomab, without HSCT.[4] Meanwhile, several clinical trials including molecular-targeted medicines combined with CAR-T treatment have been performed or are now in progress. For instance, a clinical trial at our center conducted among 18 newly diagnosed patients with Ph-positive ALL indicated that 16 patients maintained hematological complete responses within 13.5 months after achieving remission with dasatinib and glucocorticoid, followed by CD19-CAR-T and CD22-CAR-T in succession, along with maintenance therapy of dasatinib. As a result, these individuals were spared from HSCT and conventional multiagent chemotherapy.[5] Nevertheless, there is currently no comprehensive HSCT-free strategy for Ph-negative ALL. Even within the study conducted by Litzow et al., a notable percentage (25%) of participants proceeded with HSCT. Looking ahead, the integration of CAR-T therapies, BCL-2 inhibitors, PD-1/PD-L1 inhibitors, and anti-CD22 antibody-drug conjugates aims to realize future treatment regimens that are free of the need for HSCT.

In general, BiTEs is widely used in the treatment of B-ALL due to their excellent and elegant property of specifically targeting T cells and ALL cells, providing a choice for patients who had a poor response to conventional chemotherapy or HSCT. At the beginning, BiTEs serve as an alternative or upgrade regimen of conventional chemotherapy, building a bridge for patients towards HSCT. Nowadays, an increasing number of studies have demonstrated the encouraging results of BiTEs in improving patients' prognosis during the consolidation treatment of ALL, and ongoing trials are exploring the potential of BiTEs in solid tumors. It is hoped to provide patients with treatment regimens based on BiTEs without the need of chemotherapy drugs and HSCT in the future.

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DECLARATION OF INTERESTS

The authors declare no competing interests.