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The Bottom Line

Allogeneic Stem Cell Transplantation after Salvage Inotuzumab Ozogamicin: A Happy Ending?

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Most adult patients with newly diagnosed acute lymphoblastic leukemia (ALL) can achieve complete remission (CR) after current standard multiagent chemotherapies [1]. However, up to 50% of these patients will relapse, and their prognosis remains poor [2]. Minimal residual disease (MRD) status has become a strong and independent prognostic factor in ALL, because achieving MRD negativity has consistently been associated with lower relapse rates and better survival [3,4]. At relapse, a primary goal is to regain disease control to bridge patients to an allogeneic hematopoietic stem cell transplant (HSCT), the only potential cure. A preferable salvage regimen would be one to achieve CR (especially MRD negativity) without prohibitory toxicities, as transplant-related mortality and morbidity are substantial.

Inotuzumab ozogamicin (InO), a humanized anti-CD22 monoclonal antibody conjugated to the cytotoxic antibiotic calicheamicin, was approved by the US Food and Drug Administration in 2017 for adult patients with relapsed/refractory B-cell ALL based on the randomized phase III study, INO-VATE (NCT01564784) [5]. Compared with standard intensive chemotherapies relapsed/refractory ALL patients treated with single-agent InO had significantly higher rates for CR/CR with incomplete count recovery (CRi) and MRD negativity (CR/CRi, 80.7% versus 29.4%; MRD negativity, 78.4% versus 28.1%; $P < .001$) [5]. In addition, more patients in the InO group than the standard chemotherapy group were able to proceed to transplant (41.3% versus 11.0%) [5]. On the other hand, occurrence of veno-occlusive disease (VOD) was more frequent in the InO group (22 [13%], 18 [82%] of which were grade 3 or worse) than the standard intensive chemotherapies group (<1%), raising concerns for the safety of subsequent transplant [6].

In the article accompanying this editorial, Marks et al. [7] pooled data from INO-VATE and the earlier phase I/II “Study 1010” [8]. They analyzed 132 patients with relapsed/refractory ALL who proceeded to HSCT (101 after InO, 31 after standard chemotherapy), most of whom were in first relapse and without previous transplant. At last assessment before HSCT, patients treated with InO were more likely to have achieved CR/CRi (82.2% versus 67.7%) and MRD negativity (74.3% versus 25.8%) [7]. Table 2 of Marks et al. [7] summarizes and compares the post-HSCT outcomes of patients treated with InO versus standard intensive chemotherapies. The cumulative incidence of relapse was 10.9% versus 3.2% at 100 days and 28.6% versus 45.7% at 2 years ($P = .16$). The cumulative incidence of nonrelapse mortality was 21.8% versus 6.45% ($P = .01$) at 100 days and 39.3% versus 31.0% at 2 years ($P = .47$). These differences contribute to the observed survival variation over time: compared with standard intensive chemotherapies, patients treated with InO had increased mortality early but decreased mortality later after HSCT [7]. At 2 years post-HSCT, overall survival was 41.4% in the InO group versus 34.1% in the standard chemotherapy group ($P = .78$), with the highest overall survival (51.1%) in InO-treated patients who had achieved CR/CRi followed by their first HSCT [7].

VOD is a serious complication of HSCT, with >80% mortality in severe diseases [9]. VOD has been associated with older age, poorer performance status, more advanced disease (eg, relapse after prior HSCT), active hepatitis, and myeloablative conditioning regimens including busulfan and total body irradiation [10]. Marks et al. [7] reported that 19 patients (18.8%) in the InO group developed VOD after HSCT, 5 of whom (26.3%) died. Among the 19 patients, 7 (36.8%) received busulfan, 6 received dual alkylators (31.6%, including 4 who received thiotepa), and 3 received cyclophosphamide with total body irradiation (15.8%). They also found risk of VOD increased with prolonged InO treatment, from 7.1% after 1 cycle up to 23.8% after 4 to 6 cycles [7].

It is important for clinicians to be familiar with the unique adverse events related to InO. Here, we agree with the recommendations from an expert panel for preventing and monitoring VOD in patients receiving InO [11]. In transplant-eligible patients, HLA typing and donor search should be started promptly when InO is planned, with every effort to limit InO to 2 cycles before transplant. Careful selection of patients and conditioning regimen (to avoid dual alkylating agents, thiotepa, or both), high clinical vigilance (close monitoring of weight, fluid balance, and liver function tests), and timely use of prophylactic and/or therapeutic

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agents (eg, ursodiol and defibrotide) will hopefully reduce the incidence and severity of VOD.

This post hoc exploratory study is limited by the nature of the analysis, modest sample size, and lack of control for certain patient/disease characteristics (eg, cytogenetics). Nonetheless, these data provide further insight into the efficacy and safety of InO in the transplant setting and show evidence of improved long-term outcomes despite significant risk of hepatotoxicity. Compared with standard chemotherapy, InO is superior to achieve deeper remission (ie, MRD negativity) and to bridge patients to transplant, but it is far from perfect. The apparent additive clinical benefit in patients who achieved remission after InO and proceeded to their first HSCT suggests InO may be better administered early in the treatment course for relapsed/refractory ALL. It has been shown that MRD-negative status improved overall survival in InO-treated patients undergoing HSCT [12]. Therefore, patients who have achieved CR but with positive MRD after induction chemotherapy may benefit from InO to attempt to achieve MRD negativity. Blinatumomab (a bispecific T cell−engaging antibody targeting CD19 B cells) has received US Food and Drug Administration approval in this setting based on positive results from the BLAST trial [13].

InO and blinatumomab, together with chimeric antigen receptor T cell therapies, are major breakthroughs in B cell malignancies in recent years. As we continue to explore these novel therapies, more questions arise. Can we move these therapies upfront (in combination with reduced-intensity chemotherapy or even "chemotherapy-free" treatments) with hope to achieve a rapid and deep remission, so that more patients can proceed to transplant with minimized toxicities? What is the optimal combination and/or sequence of these targeted therapies, if any? Is there a role for post-transplant maintenance therapy to reduce risk of relapse? More studies are clearly needed for a better understanding of the disease, the therapies, and the strategies to improve patient outcomes.

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