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T-cell engagement in practice: bispecifics in large B-cell lymphoma

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MDS and JPA conducted the research, wrote the manuscript, and approved the final version.

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Relapsed/refractory (R/R) large B-Cell lymphoma (LBCL) remains a therapeutic challenge despite the advent of multiple novel therapeutics.[1] Chimeric antigen receptor T-cell therapy (CAR-T) remains a potentially curative option in a subset of patients; however, those with progressing disease face dismal outcomes. The approval of CD3xC20 bispecific antibodies (BsAb) glofitamab and epcoritamab have shifted the treatment landscape, providing a fast, effective off-the-shelf option, even in the post-CAR-T setting, in single-arm pivotal studies. However, safety and efficacy in unselected populations remain poorly understood.

In the accompanying article, Osborne and colleagues present a large retrospective dataset (n= 332) on the use of glofitamab and epcoritamab from 34 centers in the United Kingdom.[2] Baseline characteristics showed a predominantly heavily pretreated population with a median of 2 prior lines of therapy (range 1 to 7), 80% refractory to the last line of therapy, and 50% with prior CAR-T exposure. Importantly, only 26% of glofitamab and 17% of epcoritamab-treated patients met eligibility criteria for pivotal trials, providing a relevant analysis on the safety and efficacy of high-risk patients treated in routine clinical practice.

Interestingly, 47% of the patients received BsAb in the fourth line or beyond, and those selected for epcoritamab were more likely to have ECOG performance status ≥2 (40% vs 17%, $p<0.001$) and were less likely to have received prior CAR-T compared to the glofitamab cohort (37% vs 56%, $p=0.002$). The authors propose that this discrepancy may be related to performance status criteria on registration trials and to reimbursement issues. A wide range of pathological subtypes were included, such as transformed follicular lymphoma (tFL), T-cell/histiocyte-rich LBCL (THRLBCL), and CNS

involvement; previously underrepresented or excluded in pivotal studies. Different outcomes were observed with BsAb with an overall response rate (ORR) of 48%, CR rate of 27%, and median progression-free survival (PFS) of 5.5 months with glofitamab compared to ORR of 33%, CR rate of 17%, and median PFS of 2.9 months with epcoritamab. Stricter performance status guidelines might have been applied to glofitamab to mirror the original clinical trial inclusion criteria, so that patients with worse performance status received epcoritamab more often. Thus, a head-to-head comparison between the two agents should be interpreted cautiously for the reasons mentioned, as well as for the inherent selection bias from retrospective studies.

As expected, ORR and CRR rates were higher among trial-eligible patients and those who received at least 2 cycles of BsAb, suggesting that worse performance status may be associated with poorer outcomes due to a decreased likelihood of future cycle completion. For example, improved ORR and CR rates with glofitamab may be related to the higher number of full cycles completed over epcoritamab (3 vs 2), although the difference was small. Patients in both groups who completed cycle 2 had a median number of 4 cycles completed, with disease progression as the more common cause of treatment finalization. Another critical point to note is the definition of trial eligibility. While inclusion criteria for clinical trials should be less stringent to better reflect the highly refractory patient population they are intended to treat, patients with ECOG performance status >1 were less likely to complete cycle 2 and experienced shorter survival. Thus, while this patient subset continues to have dismal outcomes, the utility of BsAb in this highly refractory population remains to be seen, and the authors do acknowledge that better criteria are needed to truly determine which patients will benefit.

The accompanying article included a high percentage of tFL patients, showing improved CR rates and PFS compared with other subtypes, which is important information, and longer follow-up data will elucidate the durability of these responses for both histologies. Modest complete responses were observed in those with CNS involvement, and no patients with THRLBCL responded to BsAb, which has been shown to have poor outcomes after CAR-T, and now to BsAb. Factors associated with worse PFS are depicted in **Figure 1**. Prior CAR-T exposure was not independently associated with inferior response or survival, although a shorter time from CAR-T infusion to BsAb initiation was.

As the treatment options for R/R LBCL continue to evolve, the question of optimal sequencing remains a key clinical challenge. With the approval of polatuzumab-bendamustine-rituximab, many patients are exposed to bendamustine before BsAb administration, which is known to impact T-cell fitness.[3-5] Previous studies with glofitamab have highlighted the concern that administration of BsAb within 6 months of bendamustine may portend worse outcomes, showing reduced PFS, although bendamustine exposure did not retain significance in multivariate analysis.[6] In contrast, several other studies did not show a negative impact of prior bendamustine on BsAb efficacy. [7-9] Thus, worse outcomes associated with prior bendamustine exposure should be interpreted with caution, as confounding factors may account for the discrepancy between studies. Nevertheless, there remains an important area of exploration to improve understanding of how to sequence these novel agents.

Despite including a very high-risk patient population, rates of cytokine release syndrome (CRS) were low (28%) including CRS grade ≥3. ICANS occurred in 4% of patients

treated with glofitamab and 5% with epcoritamab, and infections were 48% vs 55%, respectively, in line with known clinical trial data, reinforcing the need for antibiotic prophylaxis, considering immunoglobulin replacement, and supporting the use of BsAb outside in community centers.

In summary, Osborne and colleagues should be commended for conducting this large analysis confirming that BsAb remain a well-tolerated and effective off-the-shelf option for high-risk patients in need of urgent therapy.[2] Patients who complete cycle 2 of BsAb administration have improved outcomes, including higher CR rates and PFS. Whether this is solely due to a lower disease burden and better performance status is unclear. Regardless, it remains clear that patients with multi-line refractory, high disease burden, and poor performance status continue to have worse outcomes and represent a clinical group with unmet need. Ongoing efforts to evaluate BsAb in earlier lines of therapy and to integrate them with other novel agents may prolong survival in high-risk LBCL.

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Figure legend. Factors identified in multivariable analysis associated with shorter progression-free survival.

Bendamustine exposure within six months

Refractory to prior line of therapy

Factors associated with worse progression-free survival

ECOG performance status ≥1

Elevated LDH