The Next Wave of Novel Agents in Aggressive B-Cell Lymphoma: Highlights From SOHO 2021

Kelly Valla, PharmD, BCOP, of Winship Cancer Institute of Emory University, describes the clinical implications of novel agents for aggressive B-cell lymphoma, which were described at a session presented by Gilles Salles, MD, PhD, of Memorial Sloan Kettering Cancer Center, at the 2021 SOHO Annual Meeting.

The success of blinatumomab (Blincyto) in the treatment of patients with B-cell acute lymphoblastic leukemia (ALL) is a notable advance in the management of this disease (Gökbuget et al., 2018; Kantarjian et al., 2017; Martinelli et al., 2021; Topp et al., 2015). Expanding the clinical application of bispecific antibodies across other lymphoid malignancies is a next logical step. Recent approvals including polatuzumab vedotin (Polivy), tafasitamab (Monjuvi), loncastuximab tesirine (Zynlonta), and selinexor (Xpovio) for patients with relapsed or refractory diffuse large B-cell lymphoma (DLCBL) do not clearly reflect the effort to establish a bispecific antibody in this space (Caimi et al., 2021; Kalakonda et al., 2020; Salles et al., 2020; Sehn et al., 2020). However, despite false starts, the design of easily administered, well-tolerated, and highly efficacious bispecific antibodies continues to occupy a significant space in the development of innovative treatments for DLBCL. Understanding the key features of bispecific antibodies and thereby the implications of structure on both efficacy and tolerability can assist in efforts to successfully incorporate this therapeutic strategy among previously treated patients with DLBCL.

Durable responses to the established CD19- and CD3-directed agent, blinatumomab, have been seen in DLBCL, but the story of this agent is marred by high rates of treatment discontinuation in the initial cycle of therapy (Coyle et al., 2020). In addition to treatment interruption, discontinuation, and neurologic concerns, a short half-life results in the need for continuous intravenous administration, which requires incredible care coordination and can limit the utilization to centers best equipped to meet the needs of these patients (Lee et al., 2016). Agents with longer half-lives and less cumbersome administration would vastly enhance the appetite for having a bispecific antibody in the treatment armamentarium. Furthermore, Dr. Salles explained how antibody clone selection for both T- and B-cell antibodies in the underlying structure has consequences on activity as well as toxicity. Attention to these key elements influences the power of T-cell activation and even the impact of prior or concurrent treatment with anti-CD20 therapies, which is important given the shift toward developing a CD20- and CD3-based bispecific antibody.

CLINICAL TRIAL FINDINGS

Variations in these characteristics are seen among the numerous candidate agents, including ep-

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coritamab, mosunetuzumab, odronextamab, and glofitamab. Results from the phase I/II study of epcoritamab boast a 68% overall response rate (ORR) with 45% of patients achieving complete response (CR), and an impressive 88% ORR and 38% CR rate was seen at doses of 48 mg or higher, which has been selected as the dose for further study (Hutchings et al., 2021). A phase III study comparing epcoritamab to the investigator's choice of rituximab, gemcitabine, and oxaliplatin (R-GemOx) or bendamustine and rituximab (BR) is already underway (ClinicalTrials.gov, 2021; Thieblemont et al., 2021).

Key Points

- Bispecific antibodies are promising options with high response rates and tolerable safety profiles.
- CRS and neurotoxicity from bispecific antibodies for relapsed/refractory DLBCL have been mostly low grade and tend to occur during the initiation of therapy.
- It is important for advanced practitioners to be aware of dosing schemas and how to counsel patients on symptoms to look out for.

Efficacy is also promising for mosunetuzumab (38% ORR, 20% CR), odronextamab (60% ORR, 60% CR), and glofitamab (64.3% ORR, 57.1% CR among aggressive non-Hodgkin lymphoma patients; Bannerji et al., 2020; Carlo-Stella et al., 2021; Schuster et al., 2019). Furthermore, each of the aforementioned agents is administered either intravenously or subcutaneously on an intermittent schedule.

ADVERSE EFFECTS

When evaluating the data from the standpoint of immune-mediated adverse effects, namely cytokine release syndrome (CRS) and neurotoxicity, the wait for a better bispecific antibody appears to be justified. Acceptable rates of these adverse effects are reported with all the previously mentioned candidate therapies. In the phase I/II study of epcoritamab, there were no grade 3 CRS events seen, only 3% of patients had a grade 3 neurotoxicity, and no patients discontinued therapy due to treatment-emergent adverse effects (Hutchings et al., 2021). Similarly low rates of grade 3 events have been reported with mosunetuzumab (1.4% CRS, 3.2% neurotoxicity), odronextamab (6.3% CRS, 2.3% treatment-related neurotoxicty), and glofitamab (5.8% CRS; Bannerji et al., 2020; Carlo-Stella et al., 2021; Schuster et al., 2019).

Each set of investigators report that CRS typically occurs within the first few weeks of therapy; introduction via initial step-up dosing schemas and, in the case of glofitamab, a brief lead-in with obinutuzumab (Gazyva) were utilized to mitigate CRS. Nevertheless, providers must be armed with strategies for prompt identification and management of cytokine release syndrome (CRS) and neurotoxicity as low-grade toxicity remains common. Standardization of grading through creation of the CAR T-cell toxicity (CARTOX) assessment tool and publication of guidelines outlining management strategies has been an important step toward uniform management of these notorious adverse effects (Lee et al., 2019; Neelapu et al., 2017). In fact, the team at MD Anderson Cancer Center has even developed the CARTOX app that can be downloaded for multiple operating systems, creating a modern hand-held platform to establish comfort with use of immune effector therapies outside of the most specialized centers (MD Anderson Cancer Center, n.d.).

The Advanced Practitioner Perspective

With the landscape quickly becoming crowded for relapsed/refractory DLBCL, thoughtful treatment selection should be based on factors including expected efficacy, tolerability, administration (method, frequency, and duration of therapy), and consideration of sequencing based upon prior treatments and anticipating available therapies for a subsequent relapse. At this point, ideal sequencing of newly approved agents and cellular therapy approaches (e.g., stem cell transplantation, CAR T) remains largely unknown, so introduction of another class to this space will further the need to weigh this factor.

For patients where bispecific antibodies present a viable option, advanced practitioners must be prepared to recognize and manage cytokine release syndrome (CRS) and neurotoxicity. Developing education for patients and care partners on symptoms to be on the lookout for along with ensuring there is a clear understanding of the importance and mechanism in place for reporting possible CRS or neurotoxicity are ways the advanced practitioner can play a role in the successful imple-

mentation of these immune-harnessing agents in their institutions when they are ready for prime time.

Disclosure

Dr. Valla has served on the speakers bureau for BeiGene.

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