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The Use of Glofitamab in Relapsed Diffuse Large B-Cell Lymphoma

Lorenzo Falchi, MD
Assistant Attending Physician, Lymphoma Service
Memorial Sloan Kettering Cancer Center
New York, New York

H&O What is glofitamab, and how does it work for patients with relapsed and refractory (R/R) diffuse large B-cell lymphoma (DLBCL)?

LF Glofitamab (Columvi, Genentech) is a T-cell–based immunotherapy that belongs to the class of bispecific antibodies.[1] Bispecific antibodies are bivalent, biclonal proteins that work by simultaneously binding CD20-positive target B cells and CD3-positive T cells. This interaction brings the B cells and T cells close together, resulting in a T-cell–mediated lymphoma killing. The first-in-class bispecific antibody used in hematologic malignancies was blinatumomab (Blincyto, Amgen), a CD19-directed CD3 T-cell engager.[2] Since then, several products have been developed, with glofitamab falling into the category of CD20xCD3 immunoglobulin G (IgG)-like bispecific antibodies. These products possess a full-length IgG-like structure, similar to drugs like rituximab. Pharmacokinetically, this structure allows for convenient cyclical administration either intravenously or subcutaneously, at intervals of 1 to 4 weeks. Patients with DLBCL, the most common non-Hodgkin lymphoma, typically exhibit expression of the protein CD20 on the surface of their tumor cells.[3] Therefore, when administered to patients with R/R DLBCL, glofitamab engages their T cells to seek out and destroy CD20-positive lymphoma cells.

H&O How does it compare with other bispecific antibodies approved for DLBCL?

LF There are currently 2 US Food and Drug Administration (FDA)-approved CD20xCD3 bispecific antibodies for the treatment of patients with R/R DLBCL after 2 or more systemic lines of therapy: glofitamab and epcoritamab (Epkinly, Genmab/AbbVie).[4,5] These 2 drugs are similarly potent but present some notable differences. Glofitamab has a 2:1 CD20:CD3 format, meaning that it has 2 CD20-binding moieties and one CD3 binding site, whereas epcoritamab has a 1:1 CD20:CD3 format. Additionally, glofitamab is administered intravenously, whereas epcoritamab is administered subcutaneously. The dosing schedules also vary: glofitamab is given every 3 weeks for up to 12 cycles, whereas epcoritamab is administered weekly for the first 3 cycles, then every other week from cycles 4 to 9, and finally every 4 weeks indefinitely until progression or unacceptable toxicity. Despite those differences, the results of clinical trials in terms of efficacy have been strikingly similar.

In the NP30179 study, glofitamab led to a 52% overall response rate (ORR) and a 39% complete response (CR) rate.[7] In the GEN3013-01 study, epcoritamab had a 63% ORR and a 39% CR rate (NCT03625037).[6] In both trials, approximately 40% of patients were progression-free at 12 months. In terms of safety, both bispecific

antibodies are associated with cytokine release syndrome (CRS), a systemic inflammatory reaction characterized by the overactivation of T cells that usually presents with fevers, flu-like symptoms, and, in more severe cases, hypotension and hypoxia. The rates and severity of CRS were comparable between the 2 products, with most cases being grade 1 or, less commonly, grade 2. In sum, despite the above-referenced differences, the 2 products appear to perform similarly in the clinic.

H&O What key findings have been made regarding durable responses with glofitamab?

LF Dr Hutchings recently presented results from the extended follow-up of the NP30179 trial (NCT03075696) at the 2023 American Society of Hematology (ASH) Annual Meeting.[8] Among the 154 patients with recurrent large-cell lymphoma in this pivotal phase 2 of glofitamab, 60% had received 3 or more lines of therapy, and most had disease that was refractory to the first and/or last therapy. The trial confirmed encouraging CR rates both in the overall population (40%) and in patients who had prior chimeric antigen receptor (CAR) T-cell therapy (37%). For patients who achieved a CR at the end of therapy, the median progression-free survival (PFS) was 24 months, and 66.6% were progression-free at 18 months. At the same time point, 80.7% of patients were alive and the median overall survival (OS) was not reached. There was a hint of plateau in the Kaplan-Meier curve beginning 2 years after the end of therapy. Outcomes for patients who did not achieve a CR were inferior.

The same study examined the correlation between the total metabolic tumor volume (TMTV) derived from baseline PET scans and patient outcomes. It was found that patients with a baseline TMTV lower than the median for the population had a significantly longer 24-month PFS rate than patients with a metabolic TMTV greater than the median for the population, at 41.6% vs 11.8%, respectively. Importantly, no new safety signals were detected with additional follow-up. CRS was seen in 64% of patients, mostly grade 1. Only 3% of patients had a grade 3 adverse event (AE) and 1% had a grade 4 AE, with no new AEs detected.

H&O How does glofitamab differ from other treatments for DLBCL?

LF Glofitamab and, in general, CD20xCD3 bispecific antibodies, are unique drugs, distinct from other treatments for DLBCL. The most important difference between glofitamab and classic cytotoxic chemotherapy, antibody-drug conjugates, or targeted small molecules lies in how glofitamab directly leverages a patient's immune system, specifically the CD3-positive T cells, to target tumor cells through cytotoxicity. This approach differs from traditional chemotherapy in that it is a targeted drug that solely acts on cells expressing CD20. On the other hand, glofitamab's mechanism is distinct from other drugs, like rituximab, because it does not activate the immune system broadly. It only activates CD3-positive T cells. Another crucial difference between CD20xCD3 bispecific antibodies and most other lymphoma drugs is that their activity is conditional, meaning that they are only active if the target is present. As the target cells are cleared from the body, circulating and intratumoral-activated T cells decrease accordingly because they are no longer highly engaged.

> Glofitamab has shown promise not only in DLBCL but also as a single agent or in various combinations for treating different B-cell lymphomas.

H&O What are the AEs associated with glofitamab therapy?

LF Like other CD20xCD3 bispecific antibodies, glofitamab is associated with recurrent AEs. The first is CRS. It is generally graded according to criteria published by Lee and colleagues in 2019 and, in its severe form, can require admission to the hospital for cardiopulmonary support.[9] Luckily, most cases tend to be of grade 1 or 2, indicating mild to moderate CRS. Grade 3 or 4 CRS occurrences are rare and necessitate higher levels of care, generally in the intensive care unit. The time of onset of CRS after bispecific antibody therapy varies by product and route of administration and averages 24 hours, though it can range from a few hours to a few days. Similarly, its duration, usually of 1 to 2 days, can range from less than a day to greater than a week. CRS tends to occur during cycle 1 of treatment, less frequently during cycle 2, and rarely thereafter. Specifically, with glofitamab, the first dose (a 2.5-mg priming dose) carries the highest risk of CRS. Several maneuvers have been put in place to mitigate CRS. The first strategy involves premedication before each dose, particularly during cycle 1, utilizing corticosteroids,

antihistamines, and acetaminophen. The second is to hospitalize patients during the first glofitamab dose. The third strategy employs a step-up dosing schedule during cycle 1. Instead of administering the drug at its full dose right away, a small priming dose is given first followed by an intermediate dose a week later, and then the first full dose a week after that. The fourth is to administer a single 1000-mg dose of obinutuzumab (Gazyva, Genentech) 1 week before the first glofitamab dose to decrease circulating and intratumoral B cells.[10]

The second AE is neurotoxicity, which occurs infrequently among patients treated with bispecific antibodies and often presents in a mild form. Clinically, most patients present with headaches and/or confusion, and only rarely exhibit aphasia, seizures, or coma. Management of neurotoxicity requires a multidisciplinary approach involving neurologists and/or neuro-intensivists, as appropriate.

Another important class of side effects is cytopenias, primarily neutropenia and lymphopenia. Some patients may also experience anemia and thrombocytopenia. The rates of grade 3 or 4 AEs in the pivotal clinical trial include neutropenia in 27% of cases, anemia in 6%, and thrombocytopenia in 8%. Patients are managed according to institutional standards, receiving granulocyte colony–stimulating factor and/or transfusion support as necessary.

A fourth AE is infectious complications, which are associated with the increased risks stemming from neutropenia and lymphopenia. To address this, patients are advised to undergo varicella-zoster virus prophylaxis and *Pneumocystis jirovecii* pneumonia prophylaxis throughout treatment. Granulocyte colony–stimulating factor support may be used to help manage these infectious complications effectively. Intravenous immunoglobulin replacement can also be considered in patients with symptomatic hypogammaglobulinemia because of glofitamab therapy.

H&O Any other notable studies or findings?

LF Glofitamab has shown promise not only in DLBCL but also as a single agent or in various combinations for treating different B-cell lymphomas. In the NP30179 study, glofitamab was tested as a single agent in cohorts of patients with follicular lymphoma (FL) or mantle cell lymphoma (MCL).[7] Dr Franck Morschhauser presented findings on FL and Dr Tycel Phillips presented findings on MCL at the 2021 ASH Annual Meeting.[11,12] In both cases, glofitamab demonstrated considerable activity, with promising response rates.

Moving to combination studies, a phase 3 study called STARGLO is comparing glofitamab plus gemcitabine/oxaliplatin chemotherapy (GEMOX) to rituximab plus GEMOX in patients with R/R DLBCL (NCT04408638). This trial aims to confirm and strengthen glofitamab's existing FDA approval. There is another trial combining glofitamab with ifosfamide, carboplatin, and etoposide (ICE) chemotherapy for patients with R/R DLBCL (NCT05364424).

In the frontline setting, glofitamab is being combined with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) or R-CHP-polatuzumab (Polivy, Genetech).[13,14] At the 2023 ASH Annual Meeting, Dr Max Topp updated the results of a phase 2 study that included 56 patients treated with R-CHOP-glofitamab and 24 patients treated with R-CHP-polatuzumab and yielded CR rates of 84% and 92%, respectively, with a 12-month PFS rate of 80% and 91%, respectively. The safety profile was also interesting as patients had significantly less CRS than previously seen with glofitamab, likely owing to the fact that glofitamab is introduced after 2 cycles of chemoimmunotherapy which causes tumor debulking and B cell depletion. CRS of any grade was seen in 10.7% of patients treated with R-CHOP-glofitamab and 8.3% of those receiving R-CHP-polatuzumab-glofitamab, all cases being of grade 1 or 2.[14] A second study is adding glofitamab to the R-CHOP backbone in a risk-adapted fashion. In this trial, patients undergo a baseline circulating tumor DNA (ctDNA) assessment, then receive 1 cycle of R-CHOP, followed by another ctDNA measurement, and a second cycle of R-CHOP.[13] Only patients failing to exhibit a reduction of ctDNA levels by more than 2 logs (ie, 100-fold) proceed to receive glofitamab in addition to R-CHOP. So far, the study has enrolled 29 high-risk patients. Of note, approximately 28% of them had double- or triple-hit lymphoma, a particularly difficult-to-treat entity. At the end of the study therapy, the CR rate in this group was an encouraging 85%. The safety profile confirmed that the risk of CRS was low, with an incidence of 20.7% and no grade 3 cases. Based on the promising results of these 2 trials, a randomized, controlled phase 3 studies of R-CHOP/polatuzumab with or without glofitamab is underway (NCT06047080).

H&O Are there any challenges to glofitamab therapy?

LF The first challenge is that bispecific antibodies have similarities to CAR T-cell therapy in their fundamental mode of action and safety profile.[15] Having an off-the-shelf product, such as a bispecific antibody, capable of producing encouraging results in patients who would not have other treatment options, represents a considerable advance for our patients. Despite these advances, there are still limitations in the use of these drugs. The primary challenge is treating CRS, particularly in the outpatient setting. I anticipate a learning curve being necessary as

clinicians familiarize themselves with these drugs. This will require the implementation of strict safety measures and educational efforts aimed at the physicians, their teams, the patients, and their caregivers. Another limitation is the current recommendation for patients being treated with glofitamab to be hospitalized on cycle 1, day 8 (which is when the first glofitamab dose is administered) to monitor for CRS. Although not mandatory, hospitalization during that dose is strongly recommended, particularly for providers who are new to this drug.

H&O Where are we going next?

LF Currently, 2 studies are exploring the combination of glofitamab with costimulatory bispecific antibodies. These agents provide a second signal to T cells engaged by glofitamab and amplify their activation. One of these costimulatory bispecific antibodies cotargets CD19 and 4-1BB; the other CD19 and CD28.[16-18] Early results from the 4-1BB study were presented at the ASH Annual Meeting last year, and results from the CD28 study are eagerly awaited. Results of these studies suggests that one of the main mechanisms of resistance to bispecific antibodies, which is T-cell exhaustion, can be overcome by the addition of a costimulatory molecule. We are very eager to see the additional clinical results of these studies.

Disclosures

Dr Falchi has received consulting fees and served on the advisory boards for Roche/Genentech, Genmab, AbbVie, Seagen, ADC Therapeutics, AstraZeneca, EvolveImmune, and Ipsen; and has received research funding from Roche, Genentech, Genmab, AbbVie, and Innate Pharma.

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