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The Future Role of Bispecific Antibodies in Lymphoma

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H&O What is the mechanism of action of bispecific antibodies?

JA Bispecific antibodies aim to harness the power of the immune system. These treatments are monoclonal antibodies that target 2 epitopes. One of the epitopes is on the cancer cell, and the other resides on the T cell. The bispecific antibody activates the T cell, bringing it into close proximity to the cancer cell. The T cell then kills the cancer cell.

H&O How do bispecific antibodies compare with chimeric antigen receptor (CAR) T-cell therapy?

JA Bispecific antibodies and CAR T-cell therapy activate the patient's inherent immune system, particularly T cells, to target cancer cells. The aim of both treatments is to ignite the immune system in a targeted manner against specific cancer cells. Bispecific antibodies are an off-the-shelf treatment. To produce CAR T cells, modified T cells are taken from the patient's body and then genetically modified in a laboratory to have a new receptor that targets the cancer cell. The T cells are grown and expanded. They are reinfused into the patient, following treatment with chemotherapy.

H&O What have studies of bispecific antibodies in lymphoma shown?

JA Currently, the only way to access these drugs is through clinical trials. A large amount of data from clinical trials has emerged over the past 2 to 3 years. Large numbers of patients have now been treated with these agents. We have mature follow-up data that provide insight into efficacy. The earlier studies from 3 or 4 years ago evaluated safety, toxicity, and optimal dosing. In the past 2 years, investigators have focused on finding activity in specific patient populations.

For example, epcoritamab is one of the many bispecific antibodies currently in clinical trials. At the 2022 congress of the European Hematology Association (EHA), investigators presented data from a phase 2 expansion cohort of more than 150 patients with diffuse large B-cell lymphoma (DLBCL) who received epcoritamab. The overall response rate was approximately 60%, with close to 40% of patients achieving a complete remission. The results were similar in the cohort of patients who had received prior CAR T-cell therapy. The efficacy and toxicity profiles were consistent with the early data reported for this drug, as well as for others within the class, in DLBCL.

Another bispecific antibody in development for lymphoma is called mosunetuzumab. This agent recently garnered conditional approval from the European Medicines Agency for use in relapsed and refractory follicular lymphoma. In a study presented at the 2022 EHA congress, investigators reported safety and efficacy results for patients with relapsed/refractory follicular lymphoma. They evaluated outcomes based on age in 2 cohorts: patients younger than 65 years and patients 65 years and older. The complete response rate was 55% vs 70%, respectively. Additionally, the study showed that 30% of older patients developed cytokine release syndrome

compared with 50% of younger patients, and that older patients experienced lower-grade cases of cytokine release syndrome.

I have experience with another agent, odronextamab, which has also demonstrated exceptional activity and manageable toxicity in patients with DLBCL and follicular lymphoma. The phase 1 trial results were recently published in *The Lancet Haematology*, showing complete response rates of 72% in patients with relapsed follicular lymphoma who received the highest doses of the drug. Cytokine release syndrome was noted in 61% of patients, with the vast majority experiencing only low, grade 1/2 toxicity.

Bispecific antibodies have been effective in lymphomas such as DLBCL, follicular lymphoma, and mantle cell lymphoma. Efficacy was also seen in chronic lymphocytic leukemia. Development is ongoing, particularly in diffuse large B-cell lymphoma and follicular lymphoma, where combination regimens are beginning to be explored.

Bispecific antibodies overcome several of the issues seen with CAR T-cell therapy, particularly the time-consuming process of collecting the cells from the patient, genetically modifying them, and growing them in the lab.

H&O What are the side effects of bispecific antibodies?

JA The side effects of bispecific antibodies are relatively specific to this class of drugs. In general, the agents have a similar toxicity profile that is usually based on their ability to incite cytokine release syndrome, which remains the primary concern for this drug class. As with CAR T-cell therapy, side effects can include cytokine release syndrome, fevers, low blood pressure, and liver abnormalities. Patients may develop infusion reactions. Fortunately, many of these side effects are manageable. Although the side effects seen with bispecific antibodies are similar to those reported with CAR T-cell therapy, they occur at much lower rates and with lower severity.

Bispecific antibodies are typically administered in a continuous manner. Dosing schedules include once a week, once every other week, and once a month. It appears that most of the toxicities occur within the first few weeks of treatment. After the first few weeks, the toxicity profile dramatically improves. After a month of treatment, many patients experience few side effects. There has also been a shift recently to offer these treatments for a finite duration. In many cases, the bispecific antibody is administered for 6 to 12 months, at which point patients can stop treatment. Early data suggest that this approach is feasible, with responses remaining durable after treatment cessation.

H&O How might bispecific antibodies address unmet needs in lymphoma?

JA Currently, bispecific antibodies represent a promising option for many patients. I believe that this treatment will be very relevant in the near future. In fact, the European Medicines Agency conditionally approved mosunetuzumab for use in relapsed/refractory follicular lymphoma. I anticipate that the first accelerated approvals from the US Food and Drug Administration (FDA) are expected soon. To that point, the FDA granted priority review for mosunetuzumab in patients with relapsed/refractory follicular lymphoma this past July. Bispecific antibodies address several unmet needs. In general, for patients with multiply relapsed/refractory disease, treatment options are limited and consist of chemotherapy-based regimens or monotherapy small-molecule options that offer no expectation of cure. It is known that chemotherapy is less effective in patients who have relapsed multiple times, and single-agent small molecules typically result in short duration of responses in these high-risk groups.

Immunotherapeutic approaches work very well, as shown by the experience with CAR T-cell therapy and by current data with bispecific antibodies. Several different CAR T-cell products are approved in different histologies. Initially, bispecific antibodies will likely be used in patients who have received prior lines of therapy. Bispecific antibodies provide an off-the-shelf option, so they can be used quickly. Bispecific antibodies overcome several of the issues seen with CAR T-cell therapy, particularly the time-consuming process of collecting the cells from the patient, genetically modifying them, and growing them in the laboratory. Data from clinical trials now show that bispecific antibodies can achieve responses in patients who have previously received CAR T-cell therapy, as well as in patients who have never received CAR T cells, those who are heavily pretreated, those who are

chemoresistant, and those who relapsed soon after treatment. Thus, this class of drugs holds a lot of promise to begin addressing these unmet needs.

H&O Are there any differences among the bispecific antibodies in development?

JA Many companies are developing bispecific antibodies for use in lymphoma, multiple myeloma, and even solid tumors. The bispecific antibodies have different targets based on the disease. There are different dosing schedules among the various agents, as well. Some agents can be administered subcutaneously, whereas others are administered via infusion. Our understanding of the differences among the bispecific antibodies continues to grow each year as the new data mature.

H&O Are there any challenges to overcome in the use of bispecific antibodies in lymphoma?

JA Challenges include how to optimize dosing, mitigate risks and side effects, and define the optimal treatment sequence and/or combinations with other drugs. Should bispecific antibodies be administered before or after CAR T cells? Can bispecific antibodies be used in the frontline setting, along with chemotherapy? It is not yet known how to best incorporate this new class of drugs into the treatment armamentarium. Clinical trials are currently exploring this issue.

H&O Do you have any other observations regarding the use of bispecific antibodies in lymphoma?

JA Bispecific antibodies are an exciting class of agents. I have personal experience with these drugs, and I have seen their potential power. Once bispecific antibodies receive approval from the FDA, I look forward to incorporating them into the treatment course for many of my patients outside of traditional clinical trials.

Disclosure

Dr Allan is a consultant for AbbVie, ADC Therapeutics, AstraZeneca, BeiGene, Epizyme, Genentech, Janssen, Pharmacyclics, and TG Therapeutics. He has received research funding from BeiGene, Celgene, Genentech, Janssen, and TG Therapeutics. He has received honoraria from AbbVie, AstraZeneca, BeiGene, Janssen, and Pharmacyclics.

Suggested Readings

Bannerji R, Arnason JE, Advani RH, et al. Odronextamab, a human CD20×CD3 bispecific antibody in patients with CD20-positive B-cell malignancies (ELM-1): results from the relapsed or refractory non-Hodgkin lymphoma cohort in a single-arm, multicentre, phase 1 trial. *Lancet Haematol*. 2022;9(5):e327-e339.

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Thieblemont C, Phillips T, Ghesquieres H, et al. Primary results of subcutaneous epcoritamab dose expansion in patients with relapsed or refractory large B-cell lymphoma: a phase 2 study [EHA abstract LB2364]. *HemaSphere*. 2022;6(S3).