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The Evolving Use of CAR T-Cell Therapy in Follicular Lymphoma



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H&O What clinical trial data led to the approval of chimeric antigen receptor (CAR) T-cell therapy in follicular lymphoma?

LN In March 2021, the US Food and Drug Administration (FDA) granted accelerated approval to axicabtagene ciloleucel (Yescarta, Kite) for patients with follicular lymphoma who have received at least 2 prior lines of therapy. The approval was based on results from the ZUMA-5 trial. Axicabtagene ciloleucel is an autologous CD19-directed CAR T-cell therapy with a co-stimulatory molecule of CD28. This agent was previously approved for the treatment of large-cell lymphomas, high-grade lymphomas, primary mediastinal B-cell lymphoma, and transformed follicular lymphoma. ZUMA-5 was a single-arm, multicenter phase 2 trial that enrolled patients with follicular lymphoma and marginal zone lymphoma who had received at least 2 lines of prior therapy, which had to include an anti-CD20 monoclonal antibody combined with an alkylating agent. These were patients who were heavily pretreated, with a median of 3 prior therapies. Nearly two-thirds of the patients had received 3 or more lines of therapy. They were generally young, with a median age of 60 years at enrollment. More than half of the patients had developed progressive disease within 24 months after receiving chemoimmunotherapy, a characterization known as POD24. The enrollment criteria also specified that patients were physically fit and without significant comorbidities.

Among patients with follicular lymphoma, the objective response rate was 94%, which is very high for

this heavily pretreated population. The complete response rate among the patients with follicular lymphoma was 80%. Follow-up was approximately 17 months, which is relatively short for a study of follicular lymphoma. The median progression-free survival was not reached, but it must be longer than the median follow-up of 17 months. For context, most of the FDA-approved therapies for follicular lymphoma in the third-line or later space have a median progression-free survival of approximately 11 to 14 months. In the ZUMA-5 trial, treatment with axicabtagene ciloleucel resulted in some of the best efficacy seen in relapsed follicular lymphoma to date. The durability, so far, also appears to be very promising.

H&O How is CAR T-cell therapy administered?

LN A beneficial aspect of CAR T-cell therapy is that treatment is administered once. The entire process, however, is more lengthy than that implies. First, patients must be referred to a certified center that can deliver CAR T-cell therapy. After insurance approval, they undergo leukapheresis. They are monitored during the manufacturing process, which takes on average 3 weeks with axicabtagene ciloleucel. Patients then receive a 3-day course of lymphocyte-depleting chemotherapy, which consists of fludarabine and cyclophosphamide. After a 2-day rest period, patients receive their infusion of CAR T cells. They are monitored for a minimum of 7 days.

Patients must reside within about a 2-hour drive of the treating center for up to 4 weeks, based on the Risk Evaluation and Mitigation Strategy (REMS). Although

axicabtagene ciloleucel is administered via a 1-time infusion, I generally advise patients that they will spend 6 to 8 weeks with us. After the infusion, patients are monitored for persistent toxicities, such as cytopenias. The increased risk of infection can linger for up to a year.

H&O Which types of patients with follicular lymphoma are better candidates for CAR T-cell therapy?

LN A challenge in follicular lymphoma is how to select the best treatment among the many options. The risk-stratifying tools are poor. One of the most robust indicators is POD24. One of the controversies surrounding POD24 is whether the poor prognosis is primarily driven by transformed disease. With more frequent use of positron emission tomography and/or rigorous biopsies, the population with follicular lymphoma—not transformed lymphoma—is approximately 10%. However, these patients have a poor prognosis. The ZUMA-5 trial was enriched for patients with follicular lymphoma who met the POD24 definition. This implies that investigators in the field believe that patients with POD24 represent the most critical unmet need, and CAR T-cell therapy may be a promising option for these poor-risk patients. At the 2021 American Society of Clinical Oncology meeting, there were reports on the outcomes of patients with relapsed/refractory follicular lymphoma and POD24 who were enrolled in the ZUMA-5 study. The data suggest that they do less well than those who did not meet this criterion. However, their outcomes were still quite promising.

CAR T-cell therapy should be considered for patients who are younger and are physically fit, even in the third-line setting or later. These are the patients who are expected to live a long time. It would be beneficial to give them a long interval without active disease or the need for additional therapy. My takeaway from the POD24 analysis of the ZUMA-5 study is that axicabtagene ciloleucel was associated with very favorable outcomes among those with better-risk features. In my practice, I consider CAR T-cell therapy for patients with POD24 and for young, fit patients who have quickly progressed on active treatment.

H&O How are the treatment-related toxicities managed?

LN One of the reservations about CAR T-cell therapy is the associated acute toxicities, namely, cytokine-release syndrome and immune effector cell–associated neurotoxicity syndrome (ICANS). Patients are at highest risk for these toxicities within the first 2 weeks after treatment. On average, it appears that axicabtagene ciloleucel is associated with less acute toxicity among patients with

follicular lymphoma compared with the more aggressive lymphoma subtypes, such as large-cell lymphoma. The rates of grade 3 or higher cytokine-release syndrome or ICANS were lower in the ZUMA-5 trial vs other studies of axicabtagene ciloleucel, including the ZUMA-1 study of patients with refractory large B-cell lymphoma and the ZUMA-2 study of patients with relapsed or refractory mantle cell lymphoma. The risk of death as a result of acute CAR T-cell toxicity is very low. In the ZUMA-5 study, 1 patient died from an acute toxicity related to treatment (as assessed by the investigators).

Beyond those first few weeks after the infusion, patients must be monitored for late complications. Cytopenias and B-cell aplasia can increase the risk for infection. At my institution, we generally administer prophylaxis for *Pneumocystis jirovecii* pneumonia, herpes simplex virus, and varicella-zoster virus for up to a year. Given the need to monitor these patients for months to years, CAR T-cell therapy—despite being a 1-time infusion—does require chronic or long-term management.

H&O Are there any barriers to the use of CAR T-cell therapy?

LN The competing landscape is probably the biggest barrier. In addition, most patients with follicular lymphoma are managed in community oncology sites that lack access to CAR T-cell therapy. There is a critical need for experts to convey to the community which patients should be considered and at what time point.

There are some nuances to the use of CAR T-cell therapy in follicular lymphoma. Drugs such as bendamustine (Bendeka, Teva), when given in close proximity to the collection of autologous T cells, can negatively impact the efficacy of CAR T-cell therapy. For optimal sequencing of therapy, more information is needed regarding the duration between the administration of bendamustine and the collection of autologous T cells.

Phosphoinositide 3-kinase (PI3K) inhibitors are another option for patients with follicular lymphoma. When sequenced before CAR T-cell therapy, PI3K inhibitors might enhance the efficacy of those cells. There are many questions that might be answered as clinicians gain experience with CAR T-cell therapy and more real-world data emerge.

H&O Do you anticipate that the use of CAR T-cell therapy in follicular lymphoma will evolve?

LN In the short-term, we will focus on determining which patients are optimal candidates for CAR T-cell therapy. Concerns surrounding toxicity might be alleviated with well-tolerated CAR T-cell therapy. Investigators

reported preliminary results of the ELARA study, which evaluated tisagenlecleucel (Kymriah, Novartis), an autologous CAR T-cell therapy with a 4-1BB construct, in patients with relapsed or refractory follicular lymphoma. The rates of grade 3 or higher cytokine-release syndrome and neurotoxicity were low and compared very favorably with previous reports of tisagenlecleucel in aggressive lymphoma subtypes. There is an ongoing study of lisocabtagene maraleucel (Breyanzi, Bristol Myers Squibb) in follicular lymphoma. If the trends reported in large-cell lymphoma and with tisagenlecleucel continue, lisocabtagene maraleucel should be associated with a very favorable toxicity profile. If these other CAR T-cell therapies match the efficacy seen with axicabtagene ciloleucel but have a safer toxicity profile, I envision they will be prioritized, particularly if they can be administered as outpatient procedures and in more centers.

In my practice, I consider CAR T-cell therapy for patients with POD24 and for young, fit patients who have quickly progressed on active treatment.

Another area that might evolve is the use of allogeneic CAR T-cell therapies. It might be advantageous to obtain T cells from a healthy donor, such as one who has not been exposed to prior bendamustine. An added benefit would be if the CAR T-cell therapy is safer. Researchers are exploring allogeneic CAR T-cell therapy and allogeneic natural killer CAR therapy. These types of agents might provide a better safety profile, and if they can achieve enhanced efficacy, they will be impactful.

Bispecific antibodies are about to enter the treatment landscape. These agents are T-cell engagers; they eliminate the need to manipulate the patient's own T cells, thus reducing that step in manufacturing. The question will be whether bispecific antibodies should be sequenced before or after CAR T-cell therapies or replace CAR T-cell therapy altogether. Bispecific antibodies will probably be given before CAR T-cell therapies, given their wider availability and natural progression into earlier lines of treatment in combination strategies.

To summarize, I expect there will be safer CAR T-cell therapies. Clinicians will become better at identifying which patients will benefit the most from CAR T-cell

therapies. CAR T-cell therapy will likely replace stem cell transplant in the management of follicular lymphoma.

H&O Do you have any other observations regarding the use of CAR T-cell therapy in patients with follicular lymphoma?

LN We are awaiting the mature data from the prospective clinical trials. In large-cell lymphoma, for instance, CAR T-cell therapy cures approximately 40% of patients. Prior to the introduction of these novel treatments, a patient with relapsed or refractory large-cell lymphoma had an overall survival of approximately 6 months. The scenario is less dire in follicular lymphoma. Among patients with follicular lymphoma in the third-line or later space, the available therapies are associated with a median progression-free survival of approximately 12 months. The median overall survival is also good. However, if CAR T-cell therapy has the potential to cure 40% to 50% of patients with follicular lymphoma, there should be fewer reservations surrounding the safety profile. CAR T-cell therapy might be moved to earlier lines of treatment if it is possible to identify a population in whom the risk is justifiable.

Disclosure

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Suggested Readings

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