ADVANCES IN LLM

Current Developments in the Management of Leukemia, Lymphoma, and Myeloma

Section Editor: Susan O'Brien, MD

Pilot Data on Axicabtagene Ciloleucel for CNS Lymphoma

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H&O Could you describe the impetus for and design of your pilot study on axicabtagene ciloleucel for CNS lymphoma?

CJ When lymphomas that involve the central nervous system (CNS) relapse or do not respond to chemotherapy, the prognosis is very poor and patients typically experience a short overall survival (OS). Very few drugs available to treat cancer can cross the blood-brain barrier and reach cancer cells, including lymphomas in the CNS. Although chimeric antigen receptor (CAR) T-cell therapy was first US Food and Drug Administration (FDA)-approved for lymphomas outside of the CNS, it is known that these cells can travel into the CNS, causing neurologic toxicity as one of their side effects.

We hypothesized that because CAR T-cell therapy can reach the CNS, it should be able to treat cancer cells there as well. Outside the CNS, CAR T-cell therapy has revolutionized the care of B-cell malignancies, including large B-cell lymphoma (LBCL), in which it leads to complete responses (CRs) in approximately 50% of patients with highly refractory disease that did not respond to any other therapy. For 40% to 50% of these patients, these responses were durable, lasting more than 5 years, indicating a potentially curative therapy. The hope was that CAR T-cell therapy, given its impact on lymphomas outside the CNS and its ability to cross the blood-brain barrier, could have a similarly positive effect on lymphomas in the brain and spinal cord.

However, given the known incidence of neurologic toxicity as a side effect following CAR T-cell therapy, there was concern that this could be more severe in patients with lymphomas involving the brain and spinal cord. Consequently, this study was designed primarily to assess the safety of using CAR T-cell therapy, specifically axicabtagene ciloleucel (axi-cel; Yescarta, Kite), in CNS lymphoma, and secondarily to evaluate preliminary efficacy.

H&O What were the key findings?

CJ We reported preliminary data in November at the Society for NeuroOncology meeting on 18 patients. Our final report is expected to be presented this summer at a conference, followed by publication in manuscript form. That will be when all 18 enrolled patients have reached at least 1 year of follow-up. The median follow-up for these patients at the time of the report in November was 21 months; however, it was quite varied, ranging from 4.5 to 29 months.

We saw that 94% of patients responded to axi-cel, with a CR in 71%. The estimated median duration of response was 13 months, the median progression-free survival was 14 months, and median OS was not reached. This was a big improvement over what other therapies have been able to do for chemotherapy-resistant lymphomas in the brain and spinal cord. The primary endpoint was safety with a small number of patients, so the efficacy signal was second to proving that this could be a safe therapy for patients with lymphomas in the brain and spinal cord.

H&O What were the side effects?

CJ Two toxicities that we focused on were cytokine release syndrome (CRS) and immune effector cell-associated neurotoxicity syndrome (ICANS). There were no differences in the rates of CRS and ICANS between patients with lymphomas in the brain and spinal cord compared with those without lymphomas in these regions. CRS of any grade occurred in 88% of patients and CRS of grade 3 or higher occurred in none. All the CRS was grade 1 or 2, which was an improvement over what we see with lymphomas in the body. ICANS of any grade occurred in 41% of patients, which was also an improvement over other lymphomas in the body, whereas grade 3 or higher ICANS occurred in 29% of patients, which was equivalent to what we see when we treat lymphomas in the body. These numbers appeared similar and even improved compared with the expected outcomes for axi-cel. Another side effect after CAR T-cell therapy with axi-cel has been prolonged cytopenia, in which patients experience low blood counts for weeks to months after infusion. We saw this in about half of the patients at 1 month, but all instances were resolved by 3 months. The incidence of prolonged cytopenia was initially similar to what we see with axi-cel in the treatment of lymphomas in the body, yet the recovery was much faster for those with CNS lymphoma.

These data suggest that axi-cel offers the highest chance of response with the greatest potential for durable responses in CNS lymphoma.

H&O Did a patient's molecular profile influence decision-making in this study?

CJ It did not. This study was open to all patients with LBCL involving the brain and spinal cord. There were no disease-specific characteristics to determine eligibility. However, beyond safety and efficacy, we are also learning more scientific insights related to translational research.

We have partnered with Dr Leslie S. Kean's lab at Boston Children's Hospital to analyze paired blood and cerebral spinal fluid (CSF) samples from patients. Each patient on the study had an Ommaya reservoir placed, which allowed for easy drawing of fluid from the brain and spinal cord at serial time points before and after the CAR T-cell infusion. We analyzed cytokine profiles as well as profiles of immune effector cells in both the blood and CSF at the same time points. We discovered a preferential tracking of the CAR T-cell therapy over other types of immune effector cells into the CSF, and that the CAR T-cell therapy that did enter the CSF was more likely to be CD4-positive than CD8-positive. The CAR T-cell therapy that entered the CSF was also more likely to have an activated phenotype and an interferon gamma gene-expression signature than the CAR T-cell therapy in the blood. Elegant experiments suggest that this activation happens upon entry into the CNS, rather than activated T-cell therapy being more likely to enter the CNS. By further evaluating these findings, we hope to better understand how CAR T-cell therapy works, or in cases where patients did not have a sustained remission, how it fails to work. We also aim to shed light on how CAR T-cell therapy causes neurologic toxicity and to identify new druggable targets for the prevention and treatment of this side effect. This research may benefit not only patients with CNS lymphomas but also those with other types of cancers in the body.

H&O How does axi-cel compare with other existing treatment options approved for CNS lymphoma?

CJ Most approved treatment options for CNS lymphoma include chemotherapy. However, for patients who have stopped responding to chemotherapy, ongoing chemotherapy is no longer an option. Radiation therapy is an alternative, but it carries the risk of brain damage leading to significant cognitive deficits. Other drugs used, though not necessarily approved, include Bruton tyrosine kinase (BTK) inhibitors like ibrutinib (Imbruvica, Pharmacyclics/Janssen) and acalabrutinib (Calquence, AstraZeneca) and immune checkpoint inhibitors like pembrolizumab (Keytruda, Merck) and nivolumab (Opdivo, Bristol-Myers Squibb). The response rates for these drugs typically range from 20% to 50%, but the responses are very short-lived, lasting only 1 to 3 months.

In contrast, axi-cel has shown promising results, with more than 70% of patients achieving a CR and responses extending to at least 1 year with the current follow-up. As more patients reach later time points, we hope to observe an improvement in the durability of response. At present, these data suggest that axi-cel offers the highest chance of response with the greatest potential for durable responses in CNS lymphoma.

H&O What other studies are exploring the use of this agent?

CJ Axi-cel is already approved for LBCL, relapsed LBCL, and relapsed follicular lymphoma (FL). Current studies with axi-cel are focused on moving it to earlier lines of therapy, including as frontline treatment for high-risk LBCL in ZUMA-23 (NCT05605899), and second-line treatment in early relapsing FL in an arm of ZUMA-22 (NCT05371093). However, no ongoing studies are exploring its use in other unique disease contexts.

Regarding the use of CAR T-cell therapy for CNS lymphomas, Miltenyi Biotec is conducting a study with a dual antigen-targeting CAR T-cell that targets both CD19 and CD20 (NCT04792489). This study has a cohort of patients with primary and secondary CNS lymphoma. Additionally, other CAR T-cell companies in startup are aiming to target this patient population. The unique challenge of obtaining FDA approval for CAR T-cell therapy in LBCL has led newer companies to see CNS lymphoma as an opportunity, as there are currently no FDA-approved CAR T-cell products for this specific space.

H&O What changes do you see ahead for the treatment of CNS lymphoma?

CJ CAR T-cell therapy can be used to treat lymphomas of the body that later spread to the brain (secondary CNS lymphoma), but the current approvals for CAR T-cell therapy in lymphoma include a black-box warning against its use for primary CNS lymphoma, which is CNS lymphoma that originates in the brain. I hope to see studies that the FDA will be able to consider for expanding the use of CAR T-cell therapy to treat both primary and secondary CNS lymphomas. Expanding the current study into a larger patient population could potentially support such a broadening of approval. Although it is not clear if this will end up being feasible, I am hopeful that some of the companies that are starting to explore the use of their yet-to-be-approved products in this space will have success and that we will have CAR T-cell options for these CNS lymphoma patients.

Disclosure

Dr Jacobson has consulted for Kite/Gilead, Novartis, BMS/Celgene, ImmPACT Bio, Abintus Bio, Caribou Biosciences, Appia Bio, Daiichi Sankyo, MorphoSys, Ipsen, ADC Therapeutics, AbbVie, AstraZeneca, Janssen, Sana, and Synthekine; and has received research funding from Kite/Gilead and Pfizer.

Suggested Readings

Jacobson CA, Locke FL, Ma L, et al. Real-world evidence of axicabtagene ciloleucel for the treatment of large B cell lymphoma in the United States. *Transplant Cell Ther*. 2022;28(9):581.e1-581.e8.

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