

CLL IN FOCUS

Current Developments in the Management of Chronic Lymphocytic Leukemia

The Use of Chimeric Antigen T-Cell Therapy in Chronic Lymphocytic Leukemia



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H&O What options are available for patients with chronic lymphocytic leukemia (CLL) that is refractory to Bruton tyrosine kinase (BTK) inhibitors and venetoclax?

TS This is a very important question because we are starting to see refractory disease after BTK inhibition and venetoclax (Venclexta, AbbVie), although fortunately this occurs in only a small group of patients. What we typically recommend for these patients is a clinical trial using a novel agent, such as chimeric antigen receptor (CAR) T-cell therapy or bispecific antibodies. The other option is to use a phosphoinositide 3-kinase (PI3K) inhibitor, such as idelalisib (Zydelig, Gilead) or duvelisib (Copiktra, Verastem), as third-line therapy, but these agents come with a risk for autoimmune toxicities that we prefer to avoid.

H&O What is the goal of CAR T-cell therapy in CLL?

TS Unlike aggressive lymphomas, CLL is considered an incurable disease. As a result, we aim for durable, long-term remission in CLL and other low-grade B-cell lymphomas rather than cure, per se. If we can treat patients so that they do not experience relapse in the first 10 years, can that be considered a cure? We do not yet know the answer, but we hope that our patients with CLL will not need any further treatment for many years to come.

H&O What are the most important studies that have looked at the use of CAR T-cell therapy in CLL?

TS The first published study of CAR T-cell treatment was in CLL. In this study, published in the *New England Journal of Medicine* in 2011, Porter and colleagues at the University of Pennsylvania used CD19-directed CAR T-cell therapy with tisagenlecleucel (Kymriah, Novartis) to treat a man with refractory CLL; the patient was in remission at 10 months of follow-up. An article published in *Nature* earlier this year revealed that this patient, who died of COVID-19 complications in early 2021, never experienced a recurrence of CLL, and that a second patient with CLL is still free of disease more than 10 years after CAR T-cell therapy. In addition, CAR T cells were still detectable in both patients more than 10 years after infusion. The results from these first patients to be treated with CAR T-cell therapy give us some hope that we can potentially think about long-term, durable remissions or even cures in this disease.

Although CAR T-cell therapy was first used in CLL, the focus changed to aggressive large cell lymphoma (tisagenlecleucel is approved for use in relapsed or refractory B-cell precursor acute lymphoblastic leukemia and large B-cell lymphoma) before researchers again started looking at CLL. Researchers at the Fred Hutchinson Cancer Center conducted several important studies of CAR T-cell therapy in CLL, including work on monotherapy by Turtle and colleagues and work on CAR T-cell therapy plus ibrutinib (Imbruvica, Pharmacyclics/Janssen) by Gauthier and colleagues. These studies used their own form of CD19-directed T-cell therapy, JCAR014. A slightly different version of this therapy has since been commercialized as lisocabtagene maraleucel (Breyanzi, Juno/BMS), also known as liso-cel or JCAR017, which received US Food

and Drug Administration (FDA) approval in 2021 for use in refractory large B-cell lymphoma after 2 or more lines of systemic therapy. Axicabtagene ciloleucel (Yescarta, Kite), which was first approved in 2017 to treat certain types of large B-cell lymphoma, is now approved in relapsed or refractory follicular lymphoma.

The most successful study of T-cell therapy in CLL to date has been TRANSCEND CLL 004; we published phase 1 results of this study in *Blood* earlier this year. The main trial is looking at liso-cel monotherapy, whereas liso-cel in combination with ibrutinib or venetoclax is being evaluated in smaller cohorts.

In the phase 1 portion of the monotherapy study, 23 patients with relapsed or refractory CLL or small lymphocytic lymphoma (SLL) received liso-cel at either of 2 dose levels. All the patients had already received ibrutinib, and 65% had already received venetoclax as well. Most of them (83%) had high-risk features, including mutated *TP53* and del(17p)—that is to say, the majority of these patients had disease doubly refractory to novel therapies and an especially poor prognosis.

Manufacture of the CAR T cells took approximately 1 month, and patients were able to receive bridging therapy in the meantime if needed. Then they underwent 3 days of lymphodepletion with fludarabine and cyclophosphamide, followed by 2 days of rest, followed by CAR T-cell administration. The treatment was tolerated relatively well in comparison with other products used in aggressive lymphoma. Only 2 patients had grade 3 cytokine release syndrome (CRS), and no cases of grade 4 or 5 CRS occurred. Grade 3 neurotoxicity occurred in 4 patients, and grade 4 neurotoxicity occurred in 1 patient. Most of the side effects were manageable and reversible, with no toxicity-related deaths.

At the 1-month mark, 20 patients were evaluable for minimal residual disease (MRD). We found that 75% had undetectable MRD in blood and 65% had undetectable MRD in bone marrow. Of the 22 patients who were evaluable for efficacy, 82% had an overall best response and 45% had a best complete response. The number of patients whose response improved from stable disease to partial response, or from partial response to complete response, increased over the next 3 to 4 months, but the majority of responses were seen at 1 month. These are very good results for a patient population with such refractory disease. We are following the patients to see how long the remissions will last; some of the earliest patients have now gone 3 to 4 years without a relapse. In our paper, we show that the patients in whom undetectable MRD for CLL was achieved seemed to have much more durable responses and longer progression-free survival. Unfortunately, relapse with Richter transformation did occur in 4 or 5 patients who had

undetectable MRD for CLL, which shows how unfavorable their disease biology was. It is also concerning that CAR T-cell therapy could not prevent the emergence of Richter transformation, even though no CLL was found in most of the cases. We found that the higher dose seemed to show more promise without increasing toxicities, so the patients in the phase 2 portion of the study were enrolled to receive dose level 2.

A separate cohort of this study is receiving liso-cel in combination with ibrutinib. Early follow-up, presented by Dr William Wierda at the 2020 ASH annual meeting, revealed that among the first 19 patients, only 1 case of Richter transformation had emerged. The toxicity in this group seems to have been even less severe than that seen with liso-cel monotherapy, with fewer cases of grade 3 CRS and neurotoxicity events, although the numbers were small. The responses were also very encouraging. We still need longer follow-up to determine the durability of the responses, and we need to demonstrate that the benefit of a one-time treatment outweighs the inconvenience that the treatment is far more complicated than just taking a pill daily.

We want to study CAR T-cell therapy in patients who can tolerate the therapy and whose T cells have not been battered by extensive prior treatment.

H&O What additional studies of CAR T-cell therapy in CLL are being planned?

TS I am intrigued by the idea of targeting an antigen other than CD19, such as CD22, or doubly targeting the CD19/CD20 or CD19/CD22 antigens. We are planning to open another study with Bristol Myers Squibb of a CAR T-cell agent that is targeting receptor tyrosine kinase-like orphan receptor 1 (ROR1), which may also be a very useful target in CLL and some other lymphomas. CAR T-cell therapy targeting the B-cell activating factor receptor (BAFF-R) is also under study in some lymphomas here at City of Hope. I am interested in testing that approach in CLL as well, in which we see a lot of BAFF-R expression.

H&O What are the challenges of using CAR T-cell therapy in CLL?

TS Multiple challenges exist. First, because CLL is chronic and low-grade, we can simply watch and wait and avoid treatment in many patients. When patients do need treatment, it is much simpler for them to take a pill rather than go through the CAR T-cell therapy manufacturing process and the associated risk for side effects. Unless we can give patients a good chance of a cure, it is hard to justify choosing this kind of intensive therapy early in treatment. That is why the studies right now are aimed at developing the use of CAR T-cell therapy in patients who are running out of treatment options because they are not responding to oral medication as well as we would like them to.

At the same time, we do not want to wait too long because then we risk the development of Richter transformation, or the possibility that the patient may not be fit enough to receive CAR T-cell therapy. I think we should design trials that balance these 2 concerns, so perhaps we can study the use of CAR T-cell therapy in patients whose disease has high-risk features and has failed to respond to 1 novel agent rather than 2 novel agents.

H&O What strategies are being studied to improve the response to CAR T-cell therapy?

TS Manufacturing platforms have improved tremendously over the past few years. Now that companies can make cells more reliably, we may see more consistent results. Other strategies are to treat patients at an earlier stage, when their T cells are healthier, and to combine CAR T-cell therapy with ibrutinib and other agents, potentially to enhance their effects.

H&O What other treatments are showing promise in CLL?

TS I am very interested in the use of bispecific antibodies to treat CLL, although these do not offer the same promise of cure that CAR T-cell therapy does. Existing bispecific antibodies target CD19 and CD20, and a trial of a bispecific antibody targeting CD37 is opening at City of Hope.

Nurix Therapeutics is recruiting patients for a phase 1 study of their BTK degrader therapy NX-2127 in patients with advanced B-cell malignancies; City of Hope is one of the participating centers (NCT04830137). This agent degrades the BTK enzyme, which is interesting because it is a newer mechanism of action.

Finally, studies are looking at novel oral agents such as the BTK inhibitor pirtobrutinib (NCT04965493) and the BCL2 inhibitor lisaftoclax, also known as APG-2575 (NCT03537482), in patients with CLL.

H&O Do you see a role for allogeneic CAR T-cell therapy?

TS That would be the holy grail, to have an off-the-shelf product rather than needing to manufacture a personalized autologous CAR T-cell product for each patient—it would save time and would cost less. Early results with the product have been disappointing to me, however—I have yet to hear about any responses that are better than or even equal to those seen with liso-cel in terms of depth and durability of responses, although toxicity seems not to be an issue.

H&O Any final thoughts?

TS I would like to emphasize that it is very important to enroll patients in clinical trials, and to refer them early enough that they are still in good shape. We want to study CAR T-cell therapy in patients who can tolerate the therapy and whose T cells have not been battered by extensive prior treatment. If you have a patient with CLL that is progressing especially quickly, send them to a center that studies CAR T-cell therapy so we can figure out if they meet the eligibility requirements for a trial. Without trials for such patients, we will not advance the needle fast enough in finding a cure for CLL.

Disclosures

Dr Siddiqi has served on the speakers' bureaus of AstraZeneca, BeiGene, and Bristol Myers Squibb; and has served on the advisory boards of AstraZeneca, BeiGene, Bristol Myers Squibb, Celgene, Pharmacyclics, AbbVie, and Gilead.

Suggested Readings

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