ADVANCES IN LLM

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

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Tisagenlecleucel in Pediatric Patients With Acute Lymphoblastic Leukemia

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H&O What is tisagenlecleucel?

SM Tisagenlecleucel (Kymriah, Novartis) is an engineered T-cell therapy that uses a chimeric antigen receptor (CAR) to redirect the cytotoxic machinery of a T cell toward an antigen-expressing tumor cell. The CAR targets CD19, a protein that is expressed on the surface of B cells from early stages of development and is therefore expressed on most B-cell malignancies. Tisagenlecleucel was approved by the US Food and Drug Administration (FDA) in August 2017 for pediatric and young adult patients (≤25 years) with B-cell acute lymphoblastic leukemia (ALL) that is refractory or in second or greater relapse. In May 2018, the indication was expanded to include adults with relapsed/refractory diffuse large B-cell lymphoma (DLBCL) and high-grade B-cell lymphoma after 2 lines of therapy.

H&O What did early research show?

SM In early trials conducted at the Children's Hospital of Philadelphia (CHOP) in children with relapsed or refractory ALL, more than 90% of patients achieved a remission 1 month after receiving tisagenlecleucel (known as CTL019 in these studies). Follow-up studies included a phase 2 global trial conducted at 25 centers across the world. The remission rate was 81% in children and young adults with B-cell ALL in second or greater relapse or that was refractory to chemotherapy, confirming the feasibility of maintaining efficacy while delivering this therapy via the first global supply chain of a cell therapy product.

H&O Does tisagenlecleucel differ from other CAR T-cell therapies?

SM Many principles are shared among the CAR T-cell therapies. The overall mechanism of action is similar, but there are some slight differences in the designs. There are differences in the extracellular antibody domain and the intercellular costimulatory domain. Tisagenlecleucel uses a 4-1BB costimulatory domain. Some CAR T-cell therapies use a costimulatory domain called CD28.

> It was important to learn that it is possible to export CAR T-cell therapy to more patients and more broadly.

H&O Are pediatric patients good candidates for CAR T-cell therapies in general and tisagenlecleucel in particular?

SM Yes, pediatric patients are good candidates for CAR T-cell therapies. Potential candidates for tisagenlecleucel include patients whose disease is resistant to other therapies or relapsed after treatment. Few different forms of CAR T-cell therapies are currently in use, and the ones

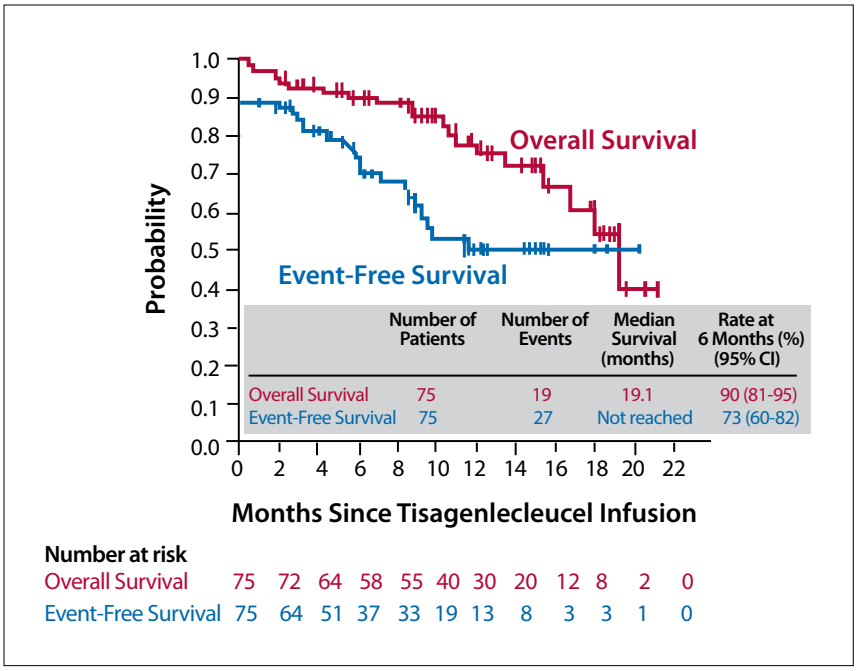

Figure. Event-free survival and overall survival in a phase 2 trial of tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. From the *New England Journal of Medicine*, Maude SL et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia, Volume 378, Pages 439-448.

that are available have a lower level of evidence than those that target CD19. We are hopeful that in the future, as the number of these therapies increase, they will expand the options for pediatric patients.

H&O Do pediatric patients with ALL pose any particular treatment challenges?

SM The field has made much progress throughout the past 50 years in reducing the rates of relapse in pediatric ALL. A remaining challenge with the currently available chemotherapies, however, is that we have reached the limit of intensity. Until recently, there was limited progress in improving outcomes for patients who had relapsed several times. Relapsed ALL, particularly that in second or greater relapse, poses a significant therapeutic challenge that we hope can be met by tisagenlecleucel and other new therapies.

H&O Could you please describe your phase 2 trial of tisagenlecleucel in pediatric and young adult patients with ALL?

SM This global, single-arm phase 2 trial was conducted at 25 centers throughout the world. The trial enrolled pediatric and young adult patients with CD19-positive relapsed or refractory B-cell ALL. The population included patients who were in second or greater relapse, patients who had relapsed after a bone marrow transplant, and patients who were refractory to chemotherapy. We analyzed the response to treatment with tisagenlecleucel. The overall remission rate within 3 months was 81%. The relapse-free survival was 80% at 6 months and 59% at 12 months (Figure).

H&O What were the adverse events?

SM The most common and serious adverse event with CD19 CAR T-cell therapies in general, and tisagenlecleucel in particular, is cytokine release syndrome. This toxicity results from a superphysiologic expansion of T cells or proliferation of T cells, leading to significant elevations in cytokines. The symptoms range from fever and flu-like symptoms to more serious and sometimes life-threatening episodes of hypotension and respiratory insufficiency. In addition, some patients experience neurotoxicity, which can include confusion, aphasia, encephalopathy and, less commonly, seizure.

H&O Were there any other notable observations from your study?

SM A finding from this study that is important for the field is that production of this highly individualized and labor-intensive therapy was performed in a centralized manufacturing facility and was able to be exported across the world. In addition, we were able to replicate results from a single-center study in a larger international, multicenter study. Previously, it was not known whether single-center results would be confirmed in

larger, multicenter studies. It was important to learn that it is possible to export CAR T-cell therapy to more patients and more broadly.

H&O How does outcome with tisagenlecleucel compare with that of other treatments in ALL?

SM Tisagenlecleucel has been studied in patients who have not responded to prior therapies. In this setting, this treatment compares very favorably with some other recently approved drugs, which have produced remission rates of 20% to 40%. Further studies will be needed to explore how the outcomes compare more broadly in other populations and against other therapies.

H&O What do you tell your patients about treatment with tisagenlecleucel?

SM We explain how tisagenlecleucel works, and we spend a significant amount of time explaining the potential side effects. We also talk about the outcomes, which are very encouraging. We mention that this therapy is still new, and that there is much to learn about longer-term outcomes and side effects.

H&O Are there any ongoing trials?

SM There are several ongoing clinical trials of tisagenlecleucel and other CD19 CAR T-cell therapies in patients with relapsed/refractory ALL at CHOP. Some ongoing trials and others in development are evaluating tisagenlecleucel and related CAR T-cell therapies in other settings in ALL, including earlier in the treatment course. In addition, we are constantly looking for ways to improve this therapy and design new CAR T-cell therapies.

Disclosure

Dr Maude has received honoraria from Novartis Pharmaceuticals.

Suggested Readings

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