Immunotherapy for T-Cell ALL and T-NHL: Highlights From SOHO 2020

In his keynote presentation, John DiPersio, MD, PhD, of Washington University, recipient of the SOHO 2020 Distinguished Lecturer Award, discussed immunotherapy for T-cell acute lymphoblastic leukemia and T-cell non-Hodgkin lymphoma. **Allyson Price, MPAS, PA-C,** of The University of Texas MD Anderson Cancer Center, distills the seminal research by Dr. DiPersio and discusses implications for advanced practitioners.

In his keynote presentation, Dr. DiPersio provided hope for the use of immunotherapy in patients with T-cell malignancies, including T-cell acute lymphoblastic leukemia (ALL) and T-cell non-Hodgkin lymphoma (T-NHL), despite the complexity of the diseases such as complex karyotype, early phenotype, and specific mutations (lack of *NOTCH* mutations, presence of *RAS* mutations). When patients relapse with these diseases, they have worse outcomes or poor prognosis.

Dr. DiPersio posed the question of how to target these T-cell malignancies with CAR T-cell therapy. The difficulty of this is that certain target antigens are shared by effector T cells and malignant T cells, resulting in fratricide. Another barrier is harvesting enough autologous T cells without contamination of malignant T cells due to the similar phenotype of these cells. There is also a significant risk of graft-vs.-host disease (GVHD) with allogenic T cells. His team hypothesized that gene editing of CAR T cells to delete target antigens and T-cell receptor alpha chain will mitigate fratricide and prevent GVHD. Therefore, they focused their efforts on CD7 since it is expressed on 98% of T cells in ALL patients and 24% of acute myeloid leukemia patients. They used third-generation CAR with CD34 epitope tag to identify and monitor through flow cytometry. They also deleted an alpha subunit (using CRISPR for gene editing). The UCART7 effectively kills T-cell ALL cell lines in vitro without the effects of GVHD. Dr. DiPersio's team used guide RNA to look at off-target effects with very minimal effects noticed, with the exception of *RBM33* ("house-keeping" gene of unclear etiology). They believe this to be relatively safe.

Key Points

- CRISPR gene editing and off-the-shelf allogeneic T cells are being studied in CAR T-cell therapy for T-cell ALL and T-NHL.
- Advanced practitioners should know about targets such as CD7 and CD2 in order to understand utilization in CAR T-cell therapy and the physiology of normal T-cell function.
- Advanced practitioners should have an understanding of CAR T-cell expansion, escape mechanisms, the limitations of CAR T-cell therapy, and GVHD.

Dr. DiPersio also discussed an approach for "CD7 antigen escape or refractory variants" by developing the UCART2, which is the "off the shelf" target CD2. CD2 is highly expressed in T-ALL and upregulated on mature T cells and natural killer cells in malignancies. This is particularly important in T-cell lymphomas that may lose their CD7 marker and because CD2 is a costimulatory molecule. There are limitations to both of these studies, including ineffective ex-

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pansion, antigen escape, and persistence in vivo. There are many approaches to expand T cells in vivo, including checkpoint inhibitors and blockades. The team used cytokine molecule NT-I7 (IL-7), which is a long-acting human interleukin that showed an increase in absolute lymphocyte count to increase efficacy with a longer half-life to enhance T-cell proliferation.

The Advanced Practitioner Perspective

This particular session was important to advanced practitioners navigating the use of CAR T-cell therapy within the patient population. It is essential to understand the basic biology of both CAR T-cell therapies to know what is being targeted and which potential complications there will be for our patients. There will be different antigen targets as these models and therapies develop. We need to understand who will be at risk for GVHD and why there can be a potential lack or loss of response from antigen escape, loss of efficacy, and difficulty with proliferation.

There continues to be discussion about where CAR T-cell therapy fits in treatment as far as relapsed setting and potential bridge to stem cell transplant. Patients will hear about CAR T-cell therapy and be curious if this is something that will benefit them, so we need to be well equipped to answer this for each individual.

Disclosure

Ms. Price has no conflicts of interest to disclose.