CAR-T Therapy Leads to Durable Response

Long-term remission seen in children with leukemia and adults with lymphoma.

December 17, 2018 By Liz Highleyman

Chimeric antigen receptor T-cell (CAR-T) therapy leads to sustained benefits for many children with leukemia and adults with lymphoma, researchers reported at the American Society of Hematology annual meeting (ASH 2018) this month in San Diego.

CAR-T therapy reprograms immune cells to recognize and attack cancer. A sample of a patient's T cells are collected and sent to a manufacturing facility, where they are genetically modified to create a customized "living drug" designed to recognize and attack their cancer. The patient's existing immune cells are killed off with strong chemotherapy and the engineered cells are reinfused. The two approved CAR-T therapies—Novartis's Kymriah (tisagenlecleucel) and Kite/Gilead's Yescarta (axicabtagene ciloleucel)— target the CD19 protein on B cells that grow out of control in people with leukemia and lymphoma.

Kymriah for Children with Leukemia

Stephan Grupp, MD, PhD, of the Children's Hospital of Philadelphia, presented two-year follow-up results from the ELIANA trial, which evaluated Kymriah in children and young adults with B-cell acute lymphoblastic leukemia.

As previously reported, 81 percent of patients achieved complete remission within three months. These findings led to the first-ever CAR-T approval in September 2017. The first child treated with Kymriah, Emily Whitehead, has now been cancer-free for more than six years.

Grupp reported longer-term follow-up data at the ASH meeting. At the time of this analysis, 97 patients were enrolled in the study and 79 had been treated with a single infusion of Kymriah (18 were not infused because of manufacturing failures, adverse events or death).

In this updated analysis, with a median 24 months of follow-up, 82 percent of treated children achieved complete response with or without complete blood count recovery within three months; all but one of them tested negative for minimal residual disease.

The median duration of response was not reached because a majority of participants were still in

remission. The estimated relapse-free survival rate at 24 months was 62 percent. The estimated overall survival rate was 76 percent at 12 months and 66 percent at 24 months. The modified CAR-T cells were still present in some responding patients for more than two and a half years, Grupp said. He added that most relapsers had CD19-negative cancer cells, suggesting they had developed resistance.

CAR-T therapy can cause potentially life-threatening side effects because the modified T cells not only kill cancer cells, but can also trigger an excessive immune response that harms healthy tissue. This cytokine release syndrome (CRS) can cause symptoms ranging from flu-like side effects to organ failure and neurotoxicity. In this study, 49 percent of patients developed severe CRS and 13 percent experienced severe neurological side effects. Most side effects occurred within the first eight weeks after infusion.

“This two-year analysis is an exciting milestone for the field, as it is the longest follow-up data for a multicenter CAR-T cell trial for those patients who have failed to respond to other treatment options,” Grupp said in a Novartis press release. “Seeing that the majority of responding patients from ELIANA are still in remission for this long after a one-time infusion further establishes Kymriah as a truly transformative treatment option.”

Kymriah for Adults with Lymphoma

Richard Maziarz, MD, of Oregon Health and Science Knight Cancer Institute in Portland, presented extended findings from the JULIET study, which tested Kymriah in adults with relapsed or refractory diffuse large B-cell lymphoma. The results were also published in The New England Journal of Medicine.

As reported at last year’s ASH meeting, the overall response rate was 53 percent in the initial analysis, including 32 percent who achieved complete remission within three months; most of those were still responding at six months.

This year, Maziarz reported that among 99 treated patients, after a median follow-up period of 19 months, the overall response rate was 54 percent, including 40 percent with complete remission. About half of patients who were partial responders at the earlier analysis became complete responders. Again, the median duration of response was not reached. The estimated 18-month relapse-free survival and overall survival rates were 64 percent and 43 percent, respectively. The median overall survival was 11.1 months overall, but was not reached for complete responders.

In this study, 23 percent developed severe CRS and 11 percent experienced severe neurological side effects. There were no deaths attributed to Kymriah, CRS, or cerebral swelling.

“CAR T therapy represents a potentially life-saving alternative for these patients, who now have a therapy that can help them achieve durable remissions even after other therapies, including transplant, have failed,” lead study author Stephen Schuster, MD, of Abramson Cancer Center at the University of Pennsylvania said in a university press release.

Yescarta for Adults with Lymphoma

Sattva Neelapu, MD, of the University of Texas MD Anderson Cancer Center in Houston, reported extended data from ZUMA-1, a study of Yescarta in adults with various types of relapsed or refractory B-cell lymphoma. The results were also published in Lancet Oncology.

Yescarta was the first CAR-T therapy approved for adults in October 2017. As previously reported, the overall response rate at nine months among participants who received a single infusion of Yescarta was 82 percent, including 54 percent with no remaining cancer. At last year's ASH meeting, Neelapu reported that after a median follow-up period of about 15 months, 42 percent of treated patients continued to respond, including 40 percent with ongoing complete remission.

This year, he reported that among 101 patients followed for 24 months, 83 percent had complete or partial responses, including 58 percent with complete remission. After a median follow-up period of 27 months, 39 percent had ongoing responses. However, the two-year ongoing response rate was much higher—93 percent—for those who were responders at one year. The median duration of response was 11.1 months overall but was not yet reached for complete responders. The median progression-free survival was 5.9 months, but the median overall survival could not yet be determined because a majority of patients were still alive.

Here, 11 percent developed severe CRS and 32 percent had severe neurological side effects. No additional treatment-related serious adverse events or deaths occurred during the extended follow-up period.

"With aggressive cancers such as refractory large B-cell lymphoma, our primary goal is to extend the lives of patients," Neelapu said in a Gilead press release. "Outcomes with traditional standard of care for this highly refractory patient population have been extremely poor. Nearly 40 percent of patients in ZUMA-1 remain in response and half of the patients are still alive after at least two years of treatment with Yescarta."

CAR-T Combinations

While the results from these three studies are good news for responders, some patients do not respond well to CAR-T therapy. Other studies presented at ASH suggest that combining CAR-T therapy with stem cell transplants or checkpoint inhibitors—which restore T-cell activity—may improve response rates.

Shannon Maude, MD, PhD, of Children's Hospital of Philadelphia presented findings from a small study of 14 children with little or no response to CAR-T therapy, early loss or poor persistence of the modified T cells or more extensive bulky disease. They received the PD-1 checkpoint inhibitors Keytruda (pembrolizumab) or Opdivo (nivolumab) starting at least two weeks after CAR-T infusion.

Children who never achieved remission after CAR-T therapy continued to progress after adding checkpoint inhibitors. However, half of those with poor CAR-T cell persistence had evidence of T cell recovery and good response, and half of those with bulky disease became complete responders.

“When we give a checkpoint inhibitor, it seems to release the immune blockade on the T cell, removing the restriction that’s holding it in check and, in turn, allowing the T cell to have greater activity,” Maude said in an ASH press release. “So in the context of CAR T cells, this combination therapy could overcome that resistance in some patients. These are children who would otherwise have no other therapeutic options, so efforts to maximize their response is critical.”

Click here to read the ELIANA ASH 2018 abstract.

Click here to read the JULIET report in The New England Journal of Medicine.

Click here to read the ZUMA-1 report in Lancet Oncology

Click here to learn more about CAR-T therapy in the Winter 2018 issue of Cancer Health.

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