Juno CAR-T Therapy Shows Durable Response for Non-Hodgkin Lymphoma

Safety profile suggests patients receiving the new immunotherapy may not need to be hospitalized.

February 2, 2018 By Liz Highleyman

Just over half of people with advanced non–Hodgkin lymphoma (NHL) who were treated with an experimental CAR-T therapy achieved complete responses, with 50 percent of those who received an optimal dose staying in remission for six months, researchers reported at the 2018 Clinical Immuno-Oncology Symposium last week in San Francisco.

Although this type of immunotherapy can sometimes lead to severe side effects, results from the TRANSCEND study suggest that some people may able to be treated as outpatients instead of being hospitalized during treatment.

Jeremy Abramson, MD, of Massachusetts General Hospital Cancer Center presented findings from a Phase I study evaluating lisocabtagene maraleucel, also known as liso-cel or JCAR017, an investigational CAR-T therapy being developed by Juno Therapeutics (recently acquired by Celgene).

Chimeric antigen receptor T-cell, or CAR-T, therapy reprograms immune cells to recognize and attack cancer. The process involves collecting a sample of a patient's T cells and sending them to a manufacturing facility, where they are genetically engineered to create a customized "living drug" for each individual. The supercharged T cells are then multiplied and infused back into the patient.

Like the two currently approved CAR-T therapies—Novartis's Kymriah (tisagenlecleucel) and Kite/Gilead's Yescarta (axicabtagene ciloleucel)—liso-cel targets the CD19 protein on B cells that grow out of control in leukemia and lymphoma. The genetically engineered product includes both modified CD4 "helper" T cells and CD8 "killer" T cells.

The ongoing TRANSCEND NHL 001 trial enrolled people with relapsed or refractory (not responsive to other treatment) aggressive B-cell non–Hodgkin lymphoma. More than 74,600 people are diagnosed with NHL and nearly 20,000 die of it in the United States each year, according to the American Cancer Society. Using available therapies, the complete response rate is less than 20 percent, according to Abramson.

The study enrolled people with various types of NHL. Abramson presented findings for a core group of 67 patients with specified types of diffuse large B-cell lymphoma (DLBCL) or high-grade B-cell lymphoma, as well as an additional 24 people with other variations including primary mediastinal B-cell lymphoma, advanced follicular lymphoma and mantle cell lymphoma.

The median age of the study participants was 61; over a third were 65 or older. They had received an average of three prior lines of treatment and half had never before achieved a complete response. Just over 40 percent had previously received stem cell transplants. Most had one or more predictors of poor survival, including so-called double- or triple-hit lymphoma.

Participants received one of two doses of liso-cel, after their existing white blood cells were killed off with strong chemotherapy to get rid of cancerous B cells and make room for the new T cells. A total of 140 people underwent a procedure called leukapheresis to collect T cells, but some were still awaiting treatment or were treated too recently to evaluate their response. Among the 91 evaluable participants, eight were treated as outpatients.

Looking first at the full group, the overall response rate at three months—meaning complete or partial tumor shrinkage—was 74 percent, including 52 percent with complete responses. Looking at the core group of patients, these rates rose to 80 percent and 55 percent, respectively, with somewhat better response among those treated with the higher liso-cel dose (81 percent and 63 percent).

The median duration of response in the core group was 9.2 months, but it was not reached among the complete responders. Of the 14 patients in the core population who received the higher dose and were followed for six months, half remained in complete remission, Abramson reported. The overall survival rate in the core group was 86 percent, rising to 94 percent for the complete responders. The median survival duration could not be determined because a majority were still alive.

Most study participants experienced adverse events after starting treatment. The most common severe side effects were low levels of white blood cells (neutropenia), red blood cells (anemia) or platelets.

CAR-T therapy can cause potentially life-threatening side effects, as unleashing modified T cells not only kills cancer cells but can also trigger an excessive immune response that harms healthy tissue. About a third of patients in the full cohort experienced cytokine release syndrome (CRS), which can cause symptoms ranging from fever to organ failure, but this was usually mild to moderate; just 1 percent had severe (grade 3 or 4) CRS. Nineteen percent developed neurotoxicity, or side effects affecting the brain, including 12 percent with severe symptoms. There were no deaths due to CRS or neurotoxicity.

The low rate of severe adverse events in this study “supports exploration of outpatient administration” of liso-cel, Abramson said.

Among the eight people treated as outpatients, one remained an outpatient throughout treatment

while others were admitted to a hospital with side effects. None experienced severe CRS or neurotoxicity; they spent fewer days hospitalized on average than those treated as inpatients (16 dversus 9 days); and none required admission to an intensive care unit.

At the same conference session, Tanya Siddiqi, MD, of City of Hope in Duarte, California, presented findings from an analysis of patient characteristics that predict liso-cel response and side effects.

Siddiqi's team found that people with a higher disease burden (larger tumors or in more locations) and higher levels of inflammatory biomarkers experienced greater expansion of the engineered T cells in their body and were more likely to develop CRS or neurotoxicity, but their responses were less durable. She suggested that the modified T cells may be more active and become exhausted in people with a high tumor burden and more inflammation. Researchers are currently studying CAR-T therapies in combination with checkpoint inhibitors and other types of immunotherapy, which could help maintain the activity of engineered T cells.

These findings suggest that testing for biomarkers may help determine which people are less likely to develop serious side effects and therefore may be good candidates for outpatient treatment.

Click here to read Abramson's abstract.

Click here to read Siddiqi's abstract.

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