Studies of personalized cell therapies define optimal doses

3 June 2016, by Steve Graff

More precise dosing methods and cellular engineering techniques show promise in the effort to improve treatment of aggressive cancers with personalized cellular therapies, according to new studies from researchers in the Perelman School of Medicine and the Abramson Cancer Center at the University of Pennsylvania and the Children's Hospital of Philadelphia. Those findings are among results of six studies of investigational chimeric antigen receptor (CAR) T cells for both adult and pediatric leukemias, adult lymphomas, and ovarian cancer which will be presented during the 2016 American Society of Clinical Oncology Annual Meeting.

Results from two clinical trials detail efforts to determine the most effective, safest dosing regimen of modified CAR T cells – which are engineered in a laboratory from patients' own T cells to hunt and potentially kill cancer cells – for adults with leukemia. Noelle Frey, MD, an assistant professor of Hematology-Oncology, will present results in 27 adult patients with acute lymphoblastic leukemia (ALL), identifying an optimal dose and infusion regimen that should improve treatment response while reducing potential for side effects.

The study's first six patients received 5 x 10^8 cells – more than 500 million of the modified cells – as a fractionated dose given over the course of three days, and five patients achieved a complete remission and one patient had a partial response to the therapy. All six had cytokine release syndrome (CRS), from which they recovered after treatment with tocilizumab, an immunosuppressant drug that blocks the effects of the inflammatory cytokine IL-6. CRS can include varying degrees of flu-like symptoms, with high fevers, nausea, and muscle pain, and temporary neurologic symptoms, including delirium, and in more severe cases, low blood pressure and breathing difficulties which may require treatment in an intensive care unit.

The next six patients received the same cell dose as a one-time infusion. Three patients in that group died of refractory CRS and sepsis, and three patients experienced complete remissions. The research team then treated 9 patients with a lower cell dose (5 x 10^7 cells), as either a one-time or a split-dose infusion. This dose was found to be safe with no treatment-related deaths, and three patients achieved a complete remission. Next, the team treated an additional 6 patients at the original higher dose split into multiple parts to closely monitor for early signs of CRS. The overall complete remission rate for patients who received this dose and schedule was 86 percent, with no treatment-related deaths. Nine of the 12 patients in those two groups experienced CRS and recovered after treatment with tocilizumab and/or steroids. The researchers say the results suggest that both the dose of T cells administered and the infusion regimen (one large dose vs several smaller doses) are important to maximize both response and safety.

In a dose-optimization study of 35 patients with chronic lymphocytic leukemia (CLL), researchers examined two different doses of CTL019 – a lower dose (5 x 10^7 cells) and a higher dose (5 x 10^8 cells). Among 30 patients who were evaluable for response, 4 of 13 responded at the lower dose (one complete remission and three partial responses, ORR = 31 percent) and nine of 17 responded at the higher dose (six complete remissions and three partial responses, ORR = 53 percent). Five patients remain in complete remission after a median follow-up of 26 months. One patient's cancer returned with CD19-negative cells, which are not amenable to targeting with CTL019. All 35 patients were evaluable for toxicity, with 19 experiencing varying degrees of CRS, four of who were treated with tocilizumab. There was no association found between cell dose and CRS development or severity. Results of this study will be presented by David Porter, MD, a professor of Hematology-Oncology and director of Blood and Marrow

Transplantation in Penn's Abramson Cancer Center.

Two studies detailing the latest results of pediatric trials of CTL019 for ALL will be presented by Shannon Maude, MD, PhD, an assistant professor of Pediatrics and a pediatric oncologist at CHOP. In a first-of-its-kind study, children who relapsed after receiving CAR T cells were re-treated with a new type of CAR engineered with a "humanized" CAR protein more closely related to human proteins than the mouse protein used in other investigational Penn and CHOP CAR T cells, in hopes of improving the modified cells' persistence in the body. The new CAR T cells, called CTL119 cells, produced complete responses in four of eight children, including one ongoing remission at seven months. Four of the eight children experienced cytokine release syndrome.

Maude will also detail updated data on pediatric ALL patients who received CTL019, expanding on results in 59 patients presented at the 57th Annual Meeting of the American Society of Hematology in December 2015. Those data showed a sustained overall response rate of 79 percent at 12 months after treatment.

In a study of 30 patients who received CTL019 for three different types of non-Hodgkin lymphoma, the researchers found that 59 percent of patients responded to the therapy (17 of 29, 15 of who experienced complete remissions of their disease). After a median follow-up of 14 months, no patients in complete remission had relapsed. These findings update results presented at December's Annual Meeting of the American Society of Hematology, with additional analysis examining the speed of patients' humoral immunity recovery following therapy. They found that over 18 months after their CTL019 treatment, counts of most patients' immunoglobulin levels (IG) –a measure of antibodies that help fight off viruses and bacteria – recovered to levels which did not require treatment with IG replacement therapy to maintain healthy immune function. The findings will be presented by Stephen Schuster, MD, the Robert and Margarita Louis-Dreyfus Associate Professor in Chronic Lymphocytic Leukemia and Lymphoma Clinical Care and Research in the Abramson Cancer Center.

In a phase I study examining the role of CAR T cells in the treatment of solid tumors, six patients with recurrent ovarian cancer received a CAR therapy directed against mesothelin (CART-meso). All six patients showed stable disease on imaging (per RECIST criteria) at one month after treatment. Tests over time showed expansion of the modified cells in the body that peaked between days seven and 10. By day 26, tests showed that cancer cells in one patient's pleural fluid had been eradicated. The CART-meso cells trafficked to tumor sites in three of four patients with available tumor samples. There were no acute adverse events related to the infusion, and no patients experienced CRS. Other symptoms observed, which may not have been related to the CART-meso infusions, included pleural effusion, breathing difficulties, abdominal pain, ascites, and constipation. These results will be presented by Janos Tanyi, MD, PhD, an assistant professor of obstetrics and gynecology.

Provided by University of Pennsylvania School of Medicine