93 percent of advanced leukemia patients in remission after immunotherapy

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Under the supervision of Dr. David Maloney, Kristin Kleinhofer receives an experimental infusion of T cells engineered to fight her cancer on Nov. 19, 2014 at Seattle Cancer Care Alliance, Fred Hutch's patient care arm. Credit: Kristin Kleinhofer

For Kristin Kleinhofer, two words—"choose hope"—have been a lifeline.

Diagnosed with leukemia in 2010, she went through treatment that put her in remission, only to have her cancer return a year and a half later, more stubborn than before. That's when she chose the phrase as her mantra, something to help her keep going. Hope buoyed her and her family as they searched for new options. And hope was what brought her to Seattle to take part in an early-phase clinical trial—one of just a handful of its kind in the nation—in which her immune cells were genetically engineered to kill her type of cancer.

"We were praying that we would get in [to this trial], and we were able to," said Kleinhofer, 41. "Then, the hope was that it would work, because there was nothing left. There were no alternative things to do. It was my last hope at the time."

On Monday, the investigators leading her immunotherapy trial published their first set of results: Kleinhofer was among the 93 percent of participants with B-cell acute lymphocytic leukemia, or ALL, who went into complete remission after their T cells were re-engineered into cancer killers—even though multiple other treatments had already failed them.

"Patients who come onto the trial have really limited options for treatment. They have refractory, acute leukemia. So the fact that we're getting so many into remission is giving these people a way forward," said study leader Dr. Cameron Turtle of Fred Hutchinson Cancer Research Center.

The paper in the *Journal of Clinical Investigation* reported on data from 30 adult ALL study participants who received the engineered cells, known as CAR T cells. The study was funded by the National Cancer Institute, Hutch spinoff Juno Therapeutics, private philanthropists and a Washington state research fund. It was designed to evaluate the cell therapy's safety and lay the groundwork for future improvements.

"In early-phase trials, you're continually learning. You don't expect results like these from early-phase trials. That's why these response rates are so extraordinary," said senior author Dr. David Maloney of Fred Hutch.

Maloney and Turtle cautioned that it is too early in this research to come to conclusions about the long-term outcomes of the patients who went into remission.

"The results are really encouraging and really exciting—and, particularly, the short-term data is really exciting—but we need more time and more research to work out what the longer-term implications of this work are," Turtle said.

'I was going to go out fighting'

Kleinhofer's cancer story began unobtrusively—with a little bump on the top of her head. She assumed it was a cyst. It was not.

In August 2010, at age 36, Kleinhofer got a call at her office in human resources at the University of California San Francisco telling her that she had ALL. From that world-shattering moment, Kleinhofer plunged into two exhausting years of chemotherapy. It bought her just a year and a half of remission.

The standard chemo regimen no longer worked, so Kleinhofer enrolled in a clinical trial of an experimental chemotherapy at Stanford. Meanwhile, her doctors began to pursue a transplant of blood-forming stem cells from bone marrow. In a transplant, a patient's cancerous blood and immune system is destroyed with chemotherapy and radiation and then replaced with healthy cells from a donor. But Kleinhofer's route to a transplant was blocked when a donor match fell through and another couldn't be found. She, her doctors and her family tried to figure out

what was next and stay optimistic that they would find another option.

"You really don't know how strong you are until something happens to you," Kleinhofer said. "No matter what, no matter where the journey led, I was going to go out fighting. I thought I would do everything I could, even if my life ended short."

Kleinhofer's doctor had once mentioned another possible option: getting her on a trial of CAR T cells. Throughout the chemo trial and search for a donor match, Kleinhofer's mother, Janet Perucca-Kleinhofer, began to look into that unfamiliar concept, with increasing excitement.

"It just makes so much sense, using one's own body to help fight cancer," Perucca-Kleinhofer said.

Kleinhofer and her mother insisted on pursuing an immunotherapy trial after the transplant match evaporated. Kleinhofer's California medical team sent out letters to investigators across the country asking if she might be eligible to enroll in their studies. In the end, there was just one that seemed to be a possibility: the Fred Hutch CAR T-cell trial.

'Like little Pac-Mans'

Like Kleinhofer, all of the trial participants had severe disease that had relapsed or was not yielding to treatment, and they had endured anywhere from one to 11 rounds of chemotherapy; 11 of them had even already had a transplant.

Patients who enroll on this trial "are extremely sick," Turtle said. "They've been through all conventional treatments that are available and likely to help them. Many of them have failed prior transplant, failed prior clinical trials. Some of them, despite their poor prognosis, are quite well when you look at them and talk to them, but others are really very,

very sick and have a very short life expectancy."

As Kleinhofer's family counted down the days until they could travel up to Seattle to try to enroll her on the trial, "I would tell you I was terrorized," Kleinhofer's mother, Perucca-Kleinhofer said. "It was the waiting—would we get in in time?"

She made it. In the fall of 2014, Kleinhofer travelled to Seattle and met with Maloney, who explained the CAR T-cell strategy and the risks of participating in the trial. She decided to enroll.

"If you're willing to take that chance, you just have to accept that 'Well, I don't know how I'm going to react, the doctors don't know how my body's going to react,'" Kleinhofer said. "But you're going to try. Because your hope is that this might be your cure. And that's what you hold on to."

To get ready for procedure, the team began engineering Kleinhofer's extracted T cells. They used a specialized virus to deliver genetic instructions into the cells for making a CAR, or chimeric antigen receptor, a synthetic molecule that allows T cells to recognize and kill cells bearing a particular marker. In this case, the CAR T cells were targeted to a marker called CD19 that is found on the surface of certain blood cells, including leukemia cells. Two weeks later, after being multiplied to the billions in the lab, Kleinhofer's new CAR T cells were ready to be infused back into her, prepared to search out and destroy her cancer.

On Nov. 19, 2014, it was CAR T-cell day.

The engineered cells were delivered to the infusion room at Seattle Cancer Care Alliance in a cooler, and the bag of clear liquid was hung up on an IV pole. Kleinhofer, her mom, and her boyfriend, Benny Juarez,

all wore their "Choose Hope" T-shirts. Nurses who had heard there was a CAR T-cell infusion going on popped into the room to watch something most of them had never seen before. Everyone was smiling for photos.

"The nurses were excited. Dr. Maloney was excited. There was a lot of excitement about this type of treatment. You don't see that excitement when you go in for chemo—the sense that this is a new technology," Juarez said.

It took less than an hour to empty the CD19-targeting CAR T cells into a vein in Kleinhofer's arm. The cells "were like little Pac-Mans, was how I imagined them, going around and eating up cancer cells," she said.

The path to remission

The CAR T-cell infusion Kleinhofer received was unique to this trial—a careful one-to-one mixture of "helper" (CD4) and "killer" (CD8) T cells, both engineered with a CD19-specific CAR that was designed and tested in the lab of trial investigator Dr. Stanley Riddell at Fred Hutch. As their names imply, the helper T cells assist the killer T cells in their mission to eradicate cells bearing the CD19 marker.

In other CAR T-cell trials, Maloney said, investigators "take whatever they can get," meaning that the specific T cells engineered with a CAR are random, and each participant could get a different mixture of the two types of cells.

By creating a CAR T-cell product with a defined composition of helper and killer cells, the researchers were able to link the dose of cells a patient received with what they experienced afterward.

"You can't work out how to go forward if you don't have any correlations between what you put into the patient and what happens to the patient,"

Turtle said. "If there's an element of random effect in the dose of the stuff you're giving or other things you're doing, it's very hard to make improvements."

Low, medium and high doses of cells all seemed to cause remissions. The CAR T cells were effective at eliminating cancer cells anywhere they appeared, the researchers reported, whether in the bone marrow or in masses throughout the body.

Of the two participants cited in the study who didn't go into remission, both had relatively little cancer in their marrow at the start of the trial. One of these ended up getting a transplant, relapsing, and rejoining the trial—and achieving remission after getting a higher T-cell dose.

Many participants experienced side effects after receiving the cells, the researchers reported. The most common side effect in the first two weeks after infusion was a condition called cytokine release syndrome, which is characterized by high fever and low blood pressure. Half of the participants also experienced confusion or other serious neurological side effects, almost all of which were temporary.

The people who were more likely to experience the most severe side effects were those who had the most cancer in their bone marrow initially and those in whom the CAR T cells multiplied most profusely after infusion, the researchers reported. In addition, the first two participants on the trial who received the highest dose of cells experienced severe toxicities, and one of these died. (A total of two patients died on the study.)

"Toxicity [from this therapy] can be severe. And we're getting a handle on it, and we hope to make it safer, and indeed, I think we have made it safer," Maloney said.

In response, the researchers changed their approach: No more participants received the highest dose level, and participants with the greatest tumor burdens were assigned to receive the lowest dose of CAR T cells. This seemed to help.

Kleinhofer said that for her, the toxicities of CAR T-cell treatment were relatively easy compared to what she'd already been through from chemotherapy, which caused everything from long-lasting fatigue to skin abscesses to heart damage. A few days after her CAR T-cell infusion, she was hospitalized for five days with cytokine release syndrome, during which time her blood pressure plummeted and she had fevers that soared to around 102, with chills and full-body aches. She'd wake up in the morning with her hospital gown drenched from sweat, and her thinking was cloudy. But it was temporary.

"Really, a week later, I felt really well. I had a lot of energy, and I actually even went and saw a couple of Seattle sights—I went to see the Space Needle for a couple hours, and the Ferris wheel," Kleinhofer said, referring to the Great Wheel on the city's downtown waterfront. "Which is really unheard of when you do regular chemo regimens. You don't have the energy or ability to do that."

'The best Christmas gift'

Kleinhofer spent another week in the hospital in December 2014 for a bacterial infection she contracted due to her chemo-weakened immune system. It was during that week that she learned the results of her CAR T-cell infusion.

"We received the awesome news that I had been placed in remission. No cancer evidence was found. And I had a chromosome abnormality that was gone, which was awesome," Kleinhofer said. "So it was perfect. It was really the best Christmas gift for me and my family."

Maloney, who oversaw Kleinhofer's care on the trial, was happy that the cells had worked just as he had hoped.

"From our perspective, we were trying to get her into remission when all these other things had failed," he said. "She was sent to us from Stanford after having failed multiple regimens in attempts to get back into remission. We gave her CAR T cells as almost like a last effort to try to do that. And it worked incredibly well, with relatively minimal toxicity."

For Kleinhofer and many other trial participants, the initial CAR T-cell infusion was not the end of their cancer ordeal. Some relapsed and were treated again with CAR T cells. Two relapsed with leukemia cells that did not bear the CD19 target recognized by the CARs.

Kleinhofer has not relapsed. But for her, the remission offered by the CAR T cells was an opportunity to get a transplant. In February 2015 at SCCA, Kleinhofer received a transplant of blood stem cells from umbilical cord blood, which is an option for people like her who cannot find a conventional adult donor match.

The trial "gave me the hope that I could proceed to get into remission so I could get a transplant," Kleinhofer said. "Which is now my next hope, that [my transplant] can give me the gift of more time until things are more figured out in the immunotherapy world."

Maloney and Turtle said that it will take long-term follow up with patients who have received a CAR T-cell infusion to figure out whether a transplant, when possible, is the best next step.

"No one really knows the answer to that question," Maloney said. "I think in some cases, CAR T cells will be enough to control the disease. But we don't have enough confidence in that yet."

Looking forward

As per Food and Drug Administration requirements for any gene therapy, the research team plans to follow up with participants for at least 15 years after they receive their CAR T cells. They are also enrolling more participants with ALL, non-Hodgkin lymphoma and chronic lymphocytic leukemia in the study. A sister trial in children and young adults at Seattle Children's Hospital is also recruiting.

In the meantime, the investigators are also already implementing improvements to the therapy.

"This is just the beginning," Turtle said. "It sounds fantastic to say that we get over 90 percent remissions, but there's so much more work to do make sure they're durable remissions, to work out who's going to benefit the most, and extend this work to other diseases."

Longer-term, Turtle said, he hopes to see this immunotherapy used against difficult-to-treat solid tumors, which can erect formidable defenses against the immune system. "It's not going to be an overnight success for those other diseases," he said. "It's going to require a lot of basic research. But that's where we're hoping it's going."

Kleinhofer is still looking forward too, optimistic about what the future holds despite the considerable challenges she's already faced—including a post-transplant infection last summer that paralyzed her. Her attitude deeply impresses Maloney, who has continued to be involved in her care from afar.

"You can't hold her down," he said. "Even when she was quadriplegic, basically, she was like, 'I'll get through this.' It's really amazing."

Kleinhofer is now walking with a cane and building her stamina to

perform everyday tasks. She wants to recover enough to visit the Greek Isles next year, a place she's always dreamed of seeing in person. And she's thinking a lot about helping others who are facing cancer, to give them the same hope that has kept her going for the past five years.

"My hope is that by educating people on everything I've learned, the immunotherapy, the cord blood, just everything, that it can help someone else in the future," she said. "Some other patient who's waiting for something, some kind of hope, some new thing that they can try to fight their cancer."

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