‘Exciting’ but Early Results in Trial of Immunotherapy for Myeloma

Cancer cells disappeared rapidly in patients with high-risk, treatment-resistant disease.

December 12, 2018 By Susan Keown

The 11 patients had already received treatment after treatment for their cancers, some as many as 20 different courses of therapy. Yet their myelomas, almost all classified by doctors as “high risk,” kept coming back. Their options faded away.

Then they joined a clinical trial to be the first people ever to receive a new experimental, immune-harnessing therapy, whose design includes features based on pioneering research at Fred Hutchinson Cancer Research Center. For several of them, this was the only trial in the world of this type of therapy for which they were eligible.

The industry-funded study was designed to find a safe dose of the experimental immunotherapy, not test its effectiveness. So these first participants got just a low dose, lower than previous studies had suggested could have much of an effect on this blood cancer.

That’s why the researchers were so encouraged when the cancerous cells vanished from every patient’s bone marrow within a month.

Trial leader Damian Green, MD, of Fred Hutch reported initial results from these first patients today at the annual meeting of the American Society of Hematology, which ran through December 11 in San Diego. The findings after an average of about five months of follow-up have him feeling “very optimistic” about the potential for this strategy.

“I think it was as good as we could have hoped for and maybe better,” said Green, a myeloma specialist. He cautioned that researchers need to study trial participants for years to draw conclusions about how well the experimental therapy will help patients in the long run.

And, he added, these “very dramatic” results don’t mean the patients are cured. In fact, the cancers of two patients on the trial came back, one to six months after they had disappeared.

However, the cancers’ unusually swift retreat in patients with few other options is “particularly exciting,” Green said, since these results represent just a starting point for this new strategy. The research team is already implementing enhancements they hope will improve results for patients.

“We’ve never seen anything like cellular adoptive immunotherapy in terms of the speed or the short time to response, and that’s very encouraging,” he said. Although there is a lot more still to learn, he said, this type of treatment “is potentially going to dramatically alter the landscape in terms of how we manage multiple myeloma.”

“Despite major advances over the past two decades, the disease almost invariably relapses. As a result, multiple myeloma experts became conditioned to avoid using the term ‘cure’ as part of our vernacular,” Green said. “As providers, we have not wanted to offer patients a false sense of hope.

“Now, in the era of immunotherapy, that sentiment may be changing.”

A unique therapy in an unusually open trial

The approach being tested in the trial, which is designed to enroll a total of 25 participants, involves genetically engineering cancer-targeting machinery into patients’ own immune cells. The tiny molecular machines are called CARs, short for chimeric antigen receptors. They are designed to empower the patients’ immune systems to home in on myeloma cells and destroy them.

On the trial, patients’ T cells, a type of immune cell, are drawn from their bloodstreams at Seattle Cancer Care Alliance, Fred Hutch’s clinical-care partner, and carried across the Hutch campus to a basement laboratory. There, the T cells are genetically engineered to produce the little CARs, multiplied to the billions, and carried back to the waiting patient by hand in a cooler days later. Then, they drip back into the patients’ bloodstreams through an IV.

The trial isn’t the first CAR-based immune therapy for multiple myeloma, nor the first to use a CAR that recognizes myeloma cells via a telltale beacon on the cancer cells known as BCMA, or B-cell maturation antigen. Several other BCMA CAR T-cell therapies have been developed by researchers around the world. Compared to the one in Green’s study, some have advanced further along in the clinical trials pipeline that can lead new treatment approaches to patients.

But there are a few unique features of Green’s trial. First, it allows an unusually wide range of patients to enroll. For example, it is the only trial of a BCMA-directed CAR T-cell product that enrolls patients whose myelomas have come back after a transplant of blood-forming stem cells from a donor — a difficult therapy that had already failed five of the 11 initial patients. The trial also enrolls patients who previously received other experimental BCMA CAR T-cell therapies on different trials.

Second, the Fred Hutch team gives participants an equal mix of two types of T cells, cell-toxic and helper T cells, which join forces to fight disease. The “defined composition” approach, as it is known, is a hallmark of Fred Hutch–designed CAR T-cell products for various kinds of cancers. Among other potential advantages, it removes a big variable — how many of each type of cell a patient receives — which makes the effects of each dose level clearer to the scientists.

Finally, as man-made molecules, CARs themselves can be assembled in an infinite number of ways. The one used in this trial is designed to optimize certain features of the cells. The final mix

of cells patients receive is produced using a Fred Hutch–specific process that was developed in the lab of Hutch scientist Stanley Riddell, MD.

No serious side effects seen — at least at low dose

In his ASH presentation, Green reported a second notable finding: Patients experienced only mild toxicities of the type associated with CAR T-cell therapies. These toxicities have the potential to be deadly.

One of them, called cytokine release syndrome, is a result of a hyperactive immune response that manifests with symptoms like high fever and low blood pressure. On this trial, one patient of the eleven experienced no cytokine release syndrome at all, and the others experienced a mild form.

Another CAR T cell–associated side effect is called neurotoxicity. It is an umbrella term for diverse neurological symptoms like delirium and headache. The research team has only seen mild and reversible neurotoxicity in the trial participants so far, Green reported.

However, this type of early trial is designed to slowly increase the dose of an experimental treatment. Green noted that more toxicity may begin appearing when participants receive more cells as planned.

CAR T-cells and beyond: new approaches for patients with multiple myeloma

Green said that recent life-extending breakthroughs in myeloma care "have raised everyone's expectations — physicians and patients alike — about what may be possible. In the era of immunotherapy, our charge is to meet those expectations by developing treatments that are tolerable, durable and, possibly, curative."

Green's goal is to answer that charge. As the trial continues, he and his Hutch colleagues are delving deeply into samples from trial participants back in the lab to learn precisely how the experimental therapy succeeds or fails. These studies "will help us tremendously to understand how to make a better CAR, how to make this approach more functional," he said.

Although this trial is still in its early days, Green, Riddell and colleagues already have launched a second trial based on their laboratory work. The new trial combines the CAR T cells with a type of experimental drug called a gamma secretase inhibitor. GSIs had been previously tested for Alzheimer's disease and various cancers.

Green and Riddell and their Hutch teammates found that GSIs had a potentially powerful effect on myeloma cells: In the lab, GSIs prevented myeloma cells from shedding BCMA, the molecular beacon that makes the cells visible to the team's CAR T cells. Their studies in Petri dishes and in mice with myeloma showed that a GSI could force cancer cells to display BCMA at high levels, helping the CAR T cells kill myeloma cells better.

Green is not leading the new trial — he's named on the licensed patent application for this use of GSIs so would have a conflict of interest — but he's watching the early results with hope that they

will show promise for patients.

He's also developing other targeted strategies for myeloma that he plans to begin testing in the clinic soon. A big focus is radioimmunotherapy: drugs designed to deliver a cancer-zapping radioactive punch straight to tumor cells while leaving healthy tissues mostly untouched.

Meanwhile, Fred Hutch scientists are currently running more than a dozen different trials of experimental therapies for multiple myeloma, from new blood stem cell transplant regimens to targeted drugs.

"It's critically important for folks to understand that [CAR T-cell therapy] is one of a number of very exciting approaches that are being generated. Coming to our center allows patients to participate in CAR T-cell trials but also in other trials that are pushing the boundaries of discovery, and that may be every bit as consequential for an individual," Green said.

The clinical trial is funded by Juno Therapeutics, a Celgene company. Green receives research funding from Juno and is eligible to receive royalties associated with the use of BCMA-targeting therapies in conjunction with GSIs in myeloma.

Note: Scientists at Fred Hutch played a role in developing these discoveries, and Fred Hutch and certain of its scientists may benefit financially from this work in the future.

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