

ADVANCES IN DRUG DEVELOPMENT

Current Developments in Oncology Drug Research

Section Editor: Mark J. Ratain, MD

Genetic Engineering of T Cells in Leukemia and Lymphoma



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H&O How does chimeric antigen receptor (CAR) cell engineering of T cells work?

JK The concept is to specifically target T cells to proteins that are expressed on the tumor cells of people with leukemia, lymphoma, and other types of cancer. This targeting is done by genetically modifying T cells.

The T cells are collected from the patient or from a volunteer donor via apheresis and then modified with a gene therapy process that involves inserting a virus into the cells, usually a lentivirus or a gammaretrovirus. We usually administer a cycle of chemotherapy to the patient before infusing the engineered cells, which home in on the tumor cells. The virus carries DNA into the T cells that becomes a permanent part of the T cells' DNA. From then on, the T cell will express a protein that is the CAR molecule. The protein is derived from a monoclonal antibody, and it gives the T cell the ability to recognize a specific target. The target that has been studied most extensively is CD19.

H&O Which patients are eligible for clinical trials of T-cell engineering?

JK I am currently involved in 2 clinical trials. One is for patients with advanced B-cell malignancies who have never undergone allogeneic stem cell transplantation. In this trial, we are taking the patient's own T cells, engineering them, and reinfusing them. The patients who are eligible for this are those with chemorefractory diffuse large B-cell lymphoma who have had at least 2 prior treatments, and those with other B-cell malignancies—such as chronic

lymphocytic leukemia (CLL), follicular lymphoma, mantle cell lymphoma, and acute lymphoblastic leukemia (ALL)—who have progressive disease after at least 1 treatment. In addition, we are now requiring all CLL patients to have had ibrutinib (Imbruvica, Pharmacyclics/Janssen Biotech) in order to be eligible for our trial.

The second trial uses allogeneic transplantation, and is for patients who have B-cell malignancies that persist despite allogeneic transplantation. In this case we genetically engineer donor cells, and infuse them into the patient.

H&O Could you talk about the results of your trial using autologous anti-CD19 CAR T cells for patients who have never undergone allogeneic stem cell transplantation?

JK This work was done in close collaboration with Steven Rosenberg of the National Cancer Institute at the National Institutes of Health. We published our results on the first 8 patients from this trial in *Blood* in 2012; we had 2 complete remissions and several progression-free partial remissions. At the 2013 American Society of Hematology (ASH) meeting, we reported that the complete remissions were ongoing in these 2 patients at 31-plus months, and 1 progression-free partial remission was continuing at 45-plus months. We also presented data on 15 patients from this trial at the ASH meeting. Of these 15, we saw 7 complete responses, 5 partial responses, 1 patient with stable disease, and 3 patients who were not evaluable; 2 patients died and 1 did not return for follow-up.

The most interesting finding from this trial was our success in treating patients with large cell lymphomas,

including diffuse large B-cell lymphoma and primary mediastinal B-cell lymphoma. Most of the groups, including our own, had previously concentrated on leukemia, mostly CLL but also some ALL. We treated 9 patients with large cell lymphomas, 8 of who were chemorefractory. Out of those 8 patients, 4 had complete responses on our protocol. The longest complete response continued at 23-plus months.

Our protocol included chemotherapy with cyclophosphamide and fludarabine before the cell infusion. Side effects of treatment included fever, fatigue, headaches, low blood pressure, and hypotension, all of which were consistent with the findings of other trials using CAR engineering of T cells.

We also saw unexpected neurologic toxicities; some patients developed aphasia for several days and a few patients developed ataxia. One patient died of unknown cause, possibly a cardiac arrest caused by depressed heart function before treatment. All other toxicities reversed completely within 2 or 3 weeks. Some patients with hypotension or hypertension needed to be treated in the intensive care unit.

H&O Could you talk about the findings of your study for patients with persistent B-cell malignancies after allogeneic transplant?

JK The allogeneic study used the same CAR T-cell technique that our autologous study did, except that we obtained our T cells from the same donor who provided the stem cells. We did not administer chemotherapy to the patients in this trial because we thought they were too fragile to tolerate chemotherapy after transplantation; we simply gave them a single infusion of cells and waited for the response. We published detailed results on the first 10 patients in *Blood* in December of 2013.

Of the 10 patients, 3 had very obvious objective responses. One had a complete remission that is ongoing, one had a partial remission, and one had a large regression of CLL with tumor lysis syndrome that did not quite meet the requirements for a partial remission. Two patients in that trial had ongoing stable disease; one over 16 months and one over 9 months. The remaining 5 patients had progression of their malignancies or short periods of stable disease followed by progression of malignancy.

We did not see any severe toxicity in the allograft trials, although 2 patients developed hypotension. We were surprised to see that no patients developed graft-vs-host disease.

H&O How long does it take for patients to respond to the engineered cells?

JK The responses can be very quick. We usually see a large response in about 1 month if we are going to see a

response. Sometimes we see a good response at 1 month that continues to improve over the next few months, or at least the positron emission tomography scan results normalize over time.

H&O Could chemotherapy potentially be eliminated from the treatment regimen?

JK We have made major reductions in the chemotherapy, so our current trials include a fairly low dose. We use a standard fludarabine-cyclophosphamide regimen containing fludarabine 30 mg/m² and cyclophosphamide 300 mg/m², concurrently and for 3 days. We have no plans to eliminate the chemotherapy, however, because chemotherapy dramatically enhances the activity of T cells in the patients. This has been soundly proven in mice. When you give chemotherapy or radiation to mice before an infusion of T cells, the T cells are much more effective at eradicating the tumors, even when the chemotherapy and radiation regimens that are used do not relate to the specific type of tumor.

The reason the chemotherapy helps is that it weakens the activity of certain T cells that inhibit the body's response to the targeted CAR T cell. Chemotherapy also causes blood cytokine levels to go up, which might help enhance the activity of CAR T cells.

H&O What are the potential advantages and disadvantages of CAR cell engineering compared with standard treatment?

JK The potential advantages are the duration and stability of the responses. The fact that we have seen patients remain in remission at 31 months after treatment raises the possibility that this could be curative, although of course it is much too soon to know. Another advantage of CAR cell engineering is that cellular therapy is completely different from chemotherapy, which means that it might offer hope to patients who are refractory to chemotherapy.

The disadvantages are that this is a complicated treatment, and of course it has the toxicities that I mentioned earlier.

H&O What other important studies have looked at CAR cell engineering?

JK The trial that first showed in vivo activity of engineered CAR cells in humans was the study that we published in *Blood* in 2010. Since then, Carl June's group at the University of Pennsylvania has shown very good results with the technique in treating adults and children with CLL and ALL. Another active group is the one at Memorial Sloan-Kettering Cancer Center led by Renier

Brentjens. This group also has focused on leukemia, with great results in both CLL and ALL but particularly in ALL. There is also a group at MD Anderson Cancer Center led by Laurence Cooper that has a variety of ongoing trials. Investigators at the Fred Hutchinson Cancer Research Center in Seattle, Washington, are studying anti-CD19 CAR T-cell therapies. A group at Baylor College of Medicine that is led by Malcolm Brenner also has published important papers on CAR T-cell engineering using both allogeneic and autologous T cells.

H&O When is the earliest that CAR cell engineering of T cells might come into routine use?

JK It is hard to say, but there is a huge amount of commercial interest in this technology. Our autologous study is sponsored by Kite Pharma, the group at the University of Pennsylvania is sponsored by Novartis, and the group at the Fred Hutchinson Cancer Research Center is sponsored by Juno Therapeutics. We are definitely going to see large, industry-sponsored trials opening up within the next couple of years.

H&O What other approaches to T-cell engineering have been attempted or are being attempted?

JK One of the trials I am planning to begin this summer is for the use of CAR T-cell engineering in multiple

myeloma. Steven Rosenberg, who is someone I collaborate closely with, has a wide variety of protocols for melanoma and other solid tumors. Although CD19 is the most active target right now, at least 1 trial of pediatric malignancies is targeting CD22, which is another promising target.

Suggested Readings

- Brentjens RJ, Davila ML, Riviere I, et al. CD19-targeted T cells rapidly induce molecular remissions in adults with chemotherapy-refractory acute lymphoblastic leukemia. *Sci Transl Med.* 2013;5(177):177ra38.
- Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med.* 2013;368(16):1509-1518.
- Kochenderfer JN, Dudley ME, Carpenter RO, et al. Donor-derived CD19-targeted T cells cause regression of malignancy persisting after allogeneic hematopoietic stem cell transplantation. *Blood.* 2013;122(25):4129-4139.
- Kochenderfer JN, Dudley ME, Feldman SA, et al. B-cell depletion and remissions of malignancy along with cytokine-associated toxicity in a clinical trial of anti-CD19 chimeric-antigen-receptor-transduced T cells. *Blood.* 2012;119(12):2709-2720.
- Kochenderfer JN, Dudley ME, Kassim SH, et al. Effective treatment of chemotherapy-refractory diffuse large B-cell lymphoma with autologous T cells genetically-engineered to express an anti-CD19 chimeric antigen receptor [ASH abstract 168]. *Blood.* 2013;122(21)(suppl).
- Kochenderfer JN, Rosenberg SA. Treating B-cell cancer with T cells expressing anti-CD19 chimeric antigen receptors. *Nat Rev Clin Oncol.* 2013;10(5):267-276.
- Kochenderfer JN, Wilson WH, Janik JE, et al. Eradication of B-lineage cells and regression of lymphoma in a patient treated with autologous T cells genetically engineered to recognize CD19. *Blood.* 2010;116(20):4099-4102.
- Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med.* 2011;365(8):725-733.

Erratum

John D. Hainsworth, MD, has modified the commentary he wrote for the December 2013 issue of *Clinical Advances in Hematology & Oncology*, “Evolving understanding and management of poorly differentiated neuroendocrine tumors.” This commentary appeared with “Metastatic pancreatic poorly differentiated neuroendocrine carcinoma: current treatment considerations” by Steven Sorscher, MD. The final paragraph of the commentary now reads as follows:

No substantial improvements in the therapy of small cell lung cancer or other PDNETs have occurred in over 20 years. To improve the therapy of these neoplasms, critical “driver” molecular abnormalities must be identified and exploited. A number of candidates are currently in early clinical testing. Owing to the similar spectrum of molecular abnormalities, it is likely that new targeted drugs that are highly effective against small cell lung cancer will also have activity in the treatment of other PDNETs.

Readers are advised to download the corrected online version at www.hematologyandoncology.net.