Chimeric Antigen Receptor-Modified T Cells for Treatment of Acute Lymphoblastic Leukemia

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Acute Lymphoblastic Leukemia

Leukemia is a type of cancer that affects the blood and bone marrow of the body by turning immature blood cells into cancer cells. Acute lymphoblastic leukemia (ALL) is a particularly aggressive type of leukemia found in both kids and adults. ALL makes up about 25% of annual cancer diagnoses in patients under fifteen. ALL is a result from an overproduction of underdeveloped white blood (leukemic cells by leukemic stem cells in the blood marrow. An abnormal amount of these cells in the blood causes suppression of normal function of other cells in the blood (Figure 1). Because leukemia spreads through the bloodstream rather than centralizing in one location, traditional tumor removal and radiation therapy are not possible. Chemotherapy and stem cell transplantation, the two most common treatment options for ALL, last for at least two years, can have harmful side effects such as hair loss and weakening of the immune system, and have low cure rates. A better treatment for fighting ALL is chimeric antigen receptor-modified (CAR) T cell therapy.

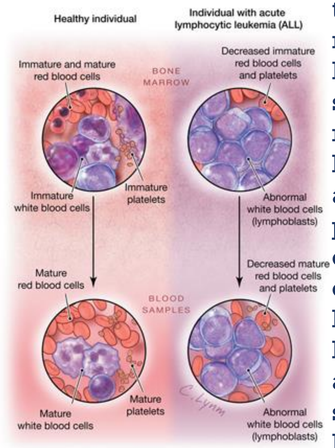

Figure 1. This diagram shows the differences in the blood an bone marrow in a health patient and in a patient with ALL.

Mechanism for CD19 CAR T Cell Therapy

Chimeric antigen receptor-modified T cell therapy functions by modifying a patient's T cells, causing the cells to express receptors that bind to specific antigens on foreign cells. Researchers have used this promising new technology to fight acute lymphoblastic leukemia by modifying T cells to express anti-CD19 receptors on their surfaces. Cells that express CD19 (an antigen found on the surface of ALL cells) are then targeted by these modified T cells, causing the T cells to latch onto the cancer. This T cell then inhibits a natural immune response, which kills and removes the unhealthy cell from the body. In a typical CAR T cell treatment, a patient's T cells are extracted and sent to a lab for manipulation. At the lab, the T cells are modified using a genetically engineered lentivirus, which inserts genes into the host's T cell DNA, causing them to express CARs . From there, these T cells are reintroduced to a patient intravenously, where they then fight cancer cells naturally (Figure 2).

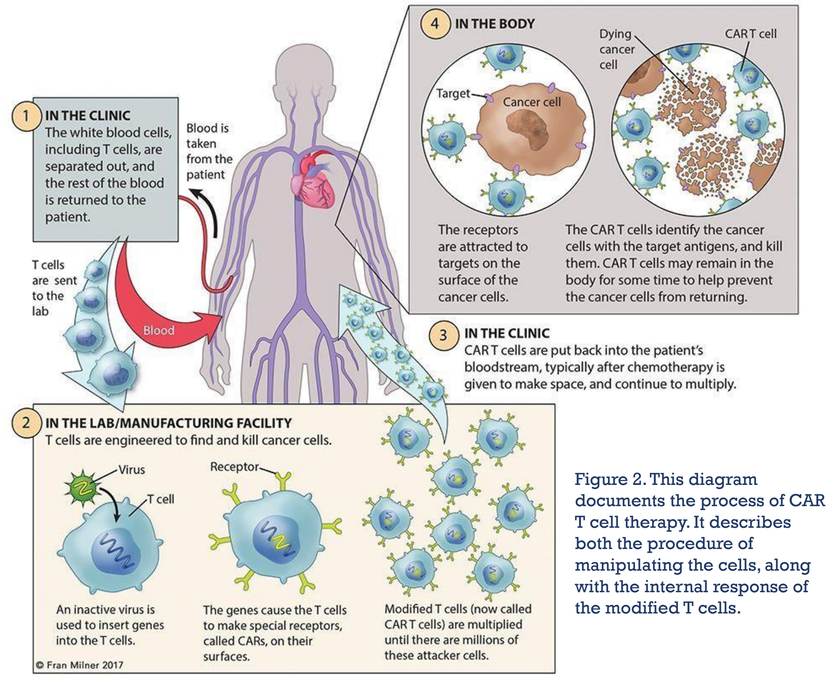

Figure 2. This diagram documents the process of CAR T cell therapy. It describes both the procedure of manipulating the cells, along with the internal response of the modified T cells.

Current Clinical Trials

Having shown significant promise in animal testing, CAR T cell therapy moved onto human clinical trials in 2014. At the University of Pennsylvania, a trial of anti-CD19 T cells on patients with ALL proved extremely successful. In the thirty patients aged five to sixty, this CAR T cell treatment, known as Eliana, showed a complete remission rate of 90% one month after infusion of the modified cells. When following the patients for an additional two years post-treatment, an overall survival rate of 78% was recorded. Although this survival rate is not significantly more than the 70% overall survival rate of ALL patients, this trial has shown promising results for CAR T cell therapy in fighting ALL. Future CAR technology aims to fight other types of cancer by identifying and targeting antigens of other cancers (Table 1).

Hematologic tumor indications	Target(s)
B cell malignancies (broad trials)	CD19, CD22, CD30, CD19/CD20 bi-specific, kappa 28
T cell malignancies (broad trials)	CD5, CD30
Acute lymphoblastic leukemia	CD19 (approved), CD22, CD19/CD22 bi-specific
Acute myeloid leukemia	CD33, CD123, NKG2D ligand
Chronic lymphocytic leukemia	CD19
Diffuse large B cell lymphoma	CD19, CD19/CD22 bi-specific
Hodgkin's lymphoma	CD19 RNA, CD30
Mantle cell lymphoma	CD19
Multiple myeloma	CD19, BCMA, MKG2D ligand
Myelodysplastic syndrome	MKG2D ligand
Non-Hodgkin lymphoma	CD19, CD20, CD30
ROR1+ malignancies	ROR1
Small lymphocytic leukemia	CD19

Note: individual indications listed may also be included in broad B cell and T cell malignancy trials.

Table 1. This table lists various cancer types and the corresponding antigen expressed on the surface of the cancerous cells.

Ethics and Sustainability

Safety

With novel medical technologies, safety is a top priority. As CAR T cell therapy progresses, researchers need to work on reducing side effects such cytokine release syndrome (CRS), which is a harmful inflammatory disease. CRS can range from being mild to life-threatening, so finding a solution to this side effect is crucial.

Access

One of the biggest concerns pertaining to the sustainability of CAR T cell therapy is its availability to patients. Only 16 states have facilities to administer this treatment, which is an issue because patients must remain within 2 hours from a treatment center for 4 months after the procedure.

Cost

CAR T cell therapy's high price tag of $475,000 presents a major ethical dilemma because it presents a barrier to mid- to low-income patients. Additionally, the current cost is not sustainable because eventually the number of people able to afford treatment will be too low to sustain the development of the technology.

Future of CAR T Cell Technology

In the future, there is hope that CAR T cell therapy will continue to be safer and more successful in patients suffering from ALL. One way that researchers have begun improving this treatment is by performing the procedure in vivo (in the body). This method of performing CAR T cell therapy, if successful, would be far more beneficial than the current in vitro (in the lab) approach. In vivo therapy research aims to create nanoparticles that can be injected into the body, manipulating T cells already present in the body to express CARs. This therapy would eliminate the time consuming and expensive task of removing a patient's T cells and manipulating them in a lab, effectively eliminating the middle man.

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