Chimeric antigen receptor (CAR) immunotherapy

Modifying a patient's T cells to seek and destroy cancer cells

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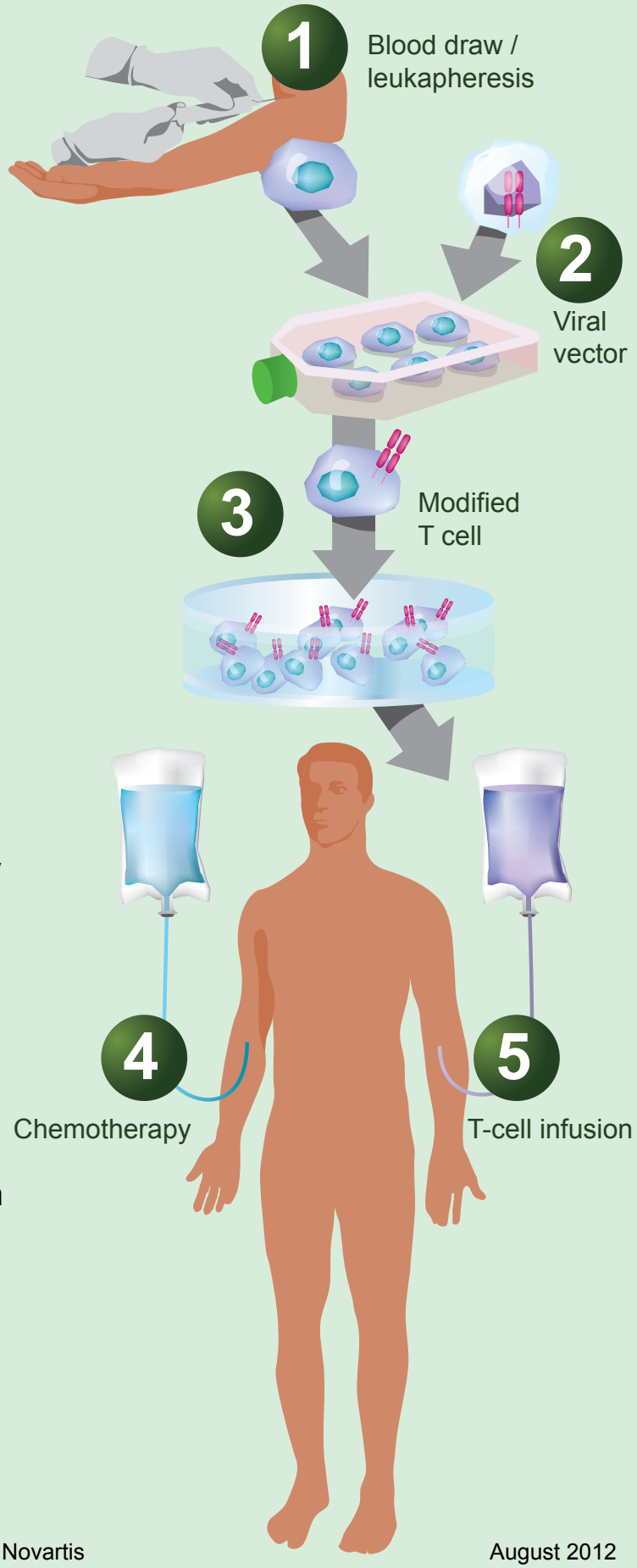
2. Genes encoded to recognize cancer cells are transferred into the patient's T cells using an inactive virus called a viral vector

3. The modified T cells are grown in the laboratory

4. The patient receives chemotherapy to reduce the level of white blood cells and help the body accept the modified T cells

5. The modified T cells are reinfused into the patient's blood, where they seek cancer cells and destroy them



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Using the body's immune system to combat cancer is not a new approach; however, decades of research have led to an increase in our understanding of immune cells (T cells) and the signals they use to attack targets effectively.

In CAR immunotherapy, in contrast to other approaches to cancer immunotherapy, T cells are drawn from a patient's blood and encoded in the laboratory with genetic instructions to seek and destroy a patient's cancer cells. When these modified T cells are infused back into the patient, they effectively become a new part of the patient's immune system specifically designed to fight the patient's cancer. CART-19 is the first therapy to have established proof of concept for this approach.

CAR Immunotherapy – Step by Step

1. **White blood cells including T cells are separated from the patient's blood, in a process called leukapheresis.** The patient's blood is drawn into a machine that separates white blood cells from the rest of the blood, and then returns red blood cells and platelets to the patient. In the laboratory, the patient's T cells are isolated from the white blood cells.

2. **Genes, encoded to recognize cancer cells, are transferred into the patient's T cells using an inactive virus.** In the laboratory, a gene is inserted into the patient's T cells using a viral vector (an inactive virus). The gene instructs the T cells to produce a protein, called a chimeric antigen receptor (CAR), on their surface. This protein gives the T cells a new ability to seek and bind to a protein (called an antigen) found on the surface of the patient's cancer cells. In the case of CART-19, the target antigen (called CD19) is associated with several B-cell malignancies, including chronic lymphocytic lymphoma, acute lymphoblastic leukemia, diffuse large B-cell lymphoma, follicular lymphoma and mantle cell lymphoma.

3. **The modified T cells are grown in the laboratory.** The modified T cells with the CARs targeting CD19 are expanded in the laboratory to produce the study therapy (CART-19).

4. **The patient receives chemotherapy to reduce the level of white blood cells and help the body accept the modified T cells.** The patient receives conventional chemotherapy to induce lymphopenia (depletion of white blood cells), as a way to create enough "space" in the body for the CART-19 cells to proliferate when they are reintroduced into the patient's blood. The choice of chemotherapy is determined by the patient's underlying disease and prior therapies.

5. **The modified T cells are reinfused into the patient's blood, where they seek cancer cells and destroy them.** When reinfused into the patient, the CART-19 cells seek and destroy the patient's cancer cells. CART-19 also produces proteins called cytokines that trigger further proliferation of the modified T cells, building a bigger and bigger army of cancer-killing immune cells over time.

About CART-19

CART-19 is a novel investigational CAR therapy. CART-19 targets a protein called CD19 that is associated with a number of B-cell malignancies such as chronic lymphocytic leukemia, B-cell acute lymphocytic leukemia and diffuse large B-cell lymphoma, among others including follicular and mantle cell lymphoma.

Early results from a clinical trial of CART-19 showed potent antileukemic effects in three patients with advanced chronic lymphocytic leukemia who had previously undergone multiple courses of chemotherapy and biological therapy. An immune deficiency known as hypogammaglobulinemia, an expected chronic toxic effect, was corrected with infusions of intravenous immune globulin. Patients were also treated for symptoms associated with tumor lysis syndrome, an effect of tumor breakdown.

Source: Porter DL, Levine BL, Kalos M, et al. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. N Engl J Med. 2011 Aug 25;365(8):725-33.

All compounds are either investigational or studied in new indications. Efficacy and safety have not been established. There is no guarantee that they will become commercially available.

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