

Innovative Immunotherapy in The Fight Against Cancer

Shankar Chakkerla

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#Advisor

ABSTRACT

Over the past century, improvements in cancer therapy treatments have accelerated in the form of immunotherapy. Immunotherapy strengthens the body's innate immune system by utilizing the full potential of T cells, an integral part of the body's immune function. In more recent years, adoptive cellular therapy which is a form of immunotherapy has become an integral part of cancer therapy because of its specificity and personalized nature. In particular, CAR therapy is making significant progress in part due to its integration of synthetic receptors onto natural T cells. This essentially allows the body's immune system to identify the advanced T-cell as one of its own but at the same time directly binding to cancer antigens and impairing the cancer cell's function to reproduce. CAR therapy is currently FDA approved to treat multiple blood cancers including lymphoma, multiple myeloma, and some forms of leukemia. CAR cells have achieved this success in blood cancers due to the antigens being present and readily detectable in the blood unlike within solid tumors wherein success is currently limited. However, with improvements in design like recognition of unique antigens, cytokine and switch receptors, and trafficking CARs, CAR T cells may ultimately be successful in treating solid tumors. These advancements can usher in a new era of lasting remission for incurable cancers in the present day.

Introduction

Cancer is the second leading cause of death globally behind heart disease. (1) It arises when the cells in our own body divide uncontrollably and destroy other body tissue. The origin of the word cancer is credited to the Greek physician Hippocrates who used the terms carcinos and carcinoma to describe non-ulcer forming and ulcer-forming tumors. (1) In Greek, these words refer to a crab, most likely refers to the finger-like spreading projections from a cancer which resembles the shape of a crab. Although the term was coined in 300 BC, some of the earliest evidence of cancer is found much earlier from around 3000 BC among fossilized bone tumors in ancient Egypt. (2) The 19th century saw the birth of scientific oncology with use of the modern techniques in studying diseased tissues with the hope of curing it and ending disease. (3)

The cornerstone of modern cancer treatments still includes surgery, radiation, and anti-neoplastic therapy. Anti-neoplastic therapy can include chemotherapy, targeted therapy, and biologic therapy. One of the most exciting applications of biologic therapy called immunotherapy has come from identifying certain tumor targets, called antigens, and aiming an antibody at these targets. This method was first used to find tumors and diagnose cancer and more recently has been used to destroy cancer cells. (4)

Immunotherapy

The use of the immune system to treat cancer begun in the nineteenth century by Wilhelm Busch and Friedrich Fehleisen. (5) William Coley, who is known as the Father of Cancer Immunotherapy, further solidified that idea

when he successfully treated cancer patients using heat-inactivated bacteria that boosted immunity. (6) Although he had developed a theory, Coley was unable to prove the significance because of a lack of significant scientific evidence and reproducibility. Fast forward to the twentieth century, scientists begun re-investigating immunotherapy using new technology. Knockout mouse models confirmed the cancer-immunosurveillance hypothesis, the idea that tumor antigens are targeted by the immune system, by showing that immunodeficiency did really lead to cancer. (2) Although immunotherapy has been known for centuries, the treatment has significant potential to grow and develop.

What is Immunotherapy?

Immune therapy is a treatment that strengthens our immune system, specifically T cells, to fight cancer cells. The three main categories of immunotherapy are:

- Immune checkpoint therapy involves blocking negative regulators of T cell activation to unleash powerful T cell responses in the immune system (7)
- Cancer vaccines are administered to reduce the chance of cancer or to harness the immune system to eliminate harmful cancer cells (8)
- Adoptive cellular therapy, one of the newest cancer treatments in its developing stages, involves the infusion of tumor fighting immune cells into the body (9)

Adoptive Cell Therapy

Because of immune-mediated responses T-cells are suppressed from performing their function. Adoptive cell therapy is designed to redirect antigen specificity and improve T-cell function. It can be broken into three categories:

- Tumor-infiltrating lymphocytes (TIL) therapy: In TIL therapy, these T cells are extracted from the body, reproduced in the lab, and modified to increase its persistence and functionality. The cells are then transferred back into the body to mediate antitumor activity and has been fairly effective in patients with epithelial cancers. (10)
- T-cell receptor (TCR) therapy: TCR therapy involves the amplification of T cells activity through the human leukocyte antigen (HLA). HLA is a gene complex that encodes cell surface proteins that essentially identify the target cells. Overexpressing the specific HLA associated with the tumor in TCR therapy facilitates the binding of antigen to peptides which is presented to T cells through the T cell receptor. (11)
- Chimeric Antigen Receptor (CAR) T therapy: CAR therapy integrates synthetic receptors into a T cell that is designed to target the antigen on the tumor cell surface. While this procedure can be more accurate, it results in higher toxicities off the target cell which can result in further complications. (12) TIL extracts T cells from the tumor directly while TCR and Car therapy isolate T cells from peripheral blood and then are redesigned to attack tumor cells via gene therapy.

CAR Therapy Treatment

Why Is It Significant/Different from Other Therapies?

CAR therapy is significant because the receptors which are binding proteins are specifically engineered to target the antigens on the surface of cancer cells. (12) They can recognize a range of antigens including carbohydrate and phospholipid antigens. This provides unique benefit because patients receive treatment that reactivates their

immune system through the introduction of a T cell that the immune system still recognizes but that can target cancer directly. This process bypasses certain non-specific immune-mediated responses that immune checkpoint blockade and other immunotherapies create which causes effects like inflammation, fever, and mucous membrane buildup.

How Is It Utilized and What Situations?

The first step of Car t-cell therapy is to extract a sample of T cells from the patient’s blood known as apheresis. The T cells are then genetically engineered using the tumor-associated antigens that are highly expressed in tumor tissue. This process, in recent years, has used CRISPR/CAS-9 techniques to improve the accuracy and efficiency of gene editing. The CAR is constructed with an intracellular domain and extracellular domain. The intracellular domain contains co-stimulation pathways such as CD28, 4-1BB or OX40 that help stimulate effector cells which are used to carry out immune functions. It also contains CD3 ζ , a protein that prevents toxicities against transformed cells. The extracellular domain is a antibody single chain which identifies the target antigen in the tumor cell. In addition to the CAR receptor, the CAR T cell is engineered to produce transgenic cytokines and equipped with chemokine receptors. Transgenic cytokines include interleukin which attracts greater anti-tumor immune cells that manage the toxicities. Chemokine receptors are located on the surface of the T cell and improve the cytotoxic function against tumor cells by shutting down immune checkpoint regulators and improving the long-term stability. (13)

Why They Are Able to Treat These Cancers?

CAR therapy has been approved by the FDA to treat blood cancers like lymphomas, some forms of leukemia, and multiple myeloma. (14) It’s been effective in these types of blood cancers because these cancers typically have one driver antigen. Thus, by implementing the antigen-specific domain into the receptor and infusing it into the body, the antigen binds to the receptor which stops future uncontrollable cell division from occurring. With the cell division on halt, the cancerous DNA no longer continues to divide. This can lead to lasting long-term remission.

FDA-Approved CAR T-Cell Therapies

Generic Name	Brand Name	Target Antigen	Targeted Disease	Patient Population
Tisagenlecleucel	Kymriah	CD19	B-cell acute lymphoblastic leukemia (ALL)	Children and young adults with refractory or relapsed B-cell ALL
			B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Axicabtagene ciloleucel	Yescarta	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
			Follicular lymphoma	Adults with relapsed or refractory follicular lymphoma
Brexucabtagene autoleucel	Tecartus	CD19	Mantle cell lymphoma (MCL)	Adults with relapsed or refractory MCL
			B-cell acute lymphoblastic leukemia (ALL)	Adults with refractory or relapsed B-cell ALL
Lisocabtagene maraleucel	Breyanzi	CD19	B-cell non-Hodgkin lymphoma (NHL)	Adults with relapsed or refractory B-cell NHL
Idecabtagene vicleucel	Abecma	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma
Ciltacabtagene autoleucel	Carvykti	BCMA	Multiple myeloma	Adults with relapsed or refractory multiple myeloma

National Cancer Institute “Car T Cells: Engineering Immune Cells to Treat Cancer”

What Are the Limitations Seen So Far?

Immune-mediated responses result from immunotherapy. Responses range based on the reactions of the body to the therapy. Common side effects include chills/fever, coughing, constipation, and fatigue. (15)

Specific side effects from adoptive cell therapy include cytokine release syndrome and immune effector cell-associated neurotoxicity syndrome. Cytokine release syndrome occurs from T-cell activation after the binding of CAR T-cells to the target. Cytokines and chemokines like IL-2 and IL-6R are produced rapidly. This happens because the immune system is so ramped up and responds to the cancer very aggressively. This can burst the tumor which causes inflammation, fever, and nausea. The primary treatment is corticosteroids that target specific cytokines like siltuximab and tocilizumab to reduce inflammation. (16)

Immune effector cell-associated neurotoxicity syndrome (ICANS) is a type of neuropsychiatric syndrome that occurs when the immune system gets out of control. It occurs in up to 67% of patients with leukemia and 62% of patients with lymphoma typically one to three weeks after CAR T cell therapy. Early symptoms are aphasia and lethargy but the symptoms can progress to seizures and even comas. Treatments to help reduce the incidence and severity of symptoms are anti-seizure medications like levetiracetam. (17)

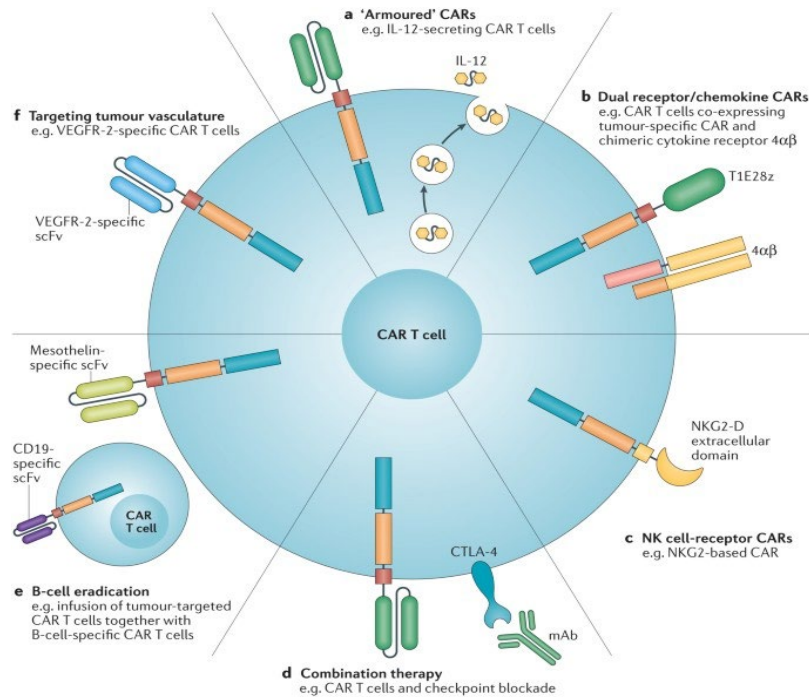
Limitations Regarding Solid Tumors

One challenge CAR T cells have is infiltrating the solid tumor microenvironment to bind to the antigen. Oftentimes, immune-suppressing molecules and other immune cells can inhibit CAR T cells and result in them malfunctioning and causing other complications. (18) Unlike tumors in the blood, there are more barriers blocking the efficacy of CAR T cells. Also, solid tumor antigens can be very similar to antigens in normal tissues which means CAR can pose as a risk to health of the normal cells in the body.

In terms of feasibility, the same cancer can have solid tumors that are composed of different antigen binding sites in different patients so the CAR T cells cannot just be reproduced to treat a group of patients. (18) Even if they express the same type of antigen, there may not be enough on certain tumor cells for the CAR T cell to recognize and bind to. Both variability and quantity of antigens pose an issue for CAR T cells to operate and work at maximum efficiency.

Discussion/Conclusions

CAR therapy has great potential for the future because it is one of the first highly personalized cancer treatments that maximizes benefit and minimizes toxicity. (19) Each CAR T cell is constructed and designed for the cancer antigen it is targeting in a given patient. In this way, it has served to provide long-term remission for specific liquid tumor cancers. The CAR has to be specific but also sensitive enough to be able to adapt to mutations that the cancer antigens may develop. to avoid recognition. This has led to the design of the CAR continually evolving especially in recent years. Specific aspects like recognition of multiple antigens to activate the receptor has improved the efficacy of CAR T cells. Other measures include implementing switch receptors and cytokine-secreting TRUCKs that increase the antitumor effect and allow T cells to overcome immunosuppression. Trafficking CARs can help improve the ability of the T cell to target a solid tumor. Lastly, CARs with on and off switches or suicide switches can help reduce toxicity and protect the other cells within patients. (20) By improving the efficacy of current measures through boosting recognition and anti-tumor response, CARs can continue to improve in treating solid tumors and ultimately provide solutions to some of cancer's most dangerous mechanisms.



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