Chimeric Antigen Receptor T-Cell Immunotherapy

Abstract

Chimeric Antigen Receptor T-Cell therapy is a definitive breakthrough in cancer treatment – it has changed the way certain cancers are managed, as a whole. By using genetically engineered T-cells to fight diseased cells, the body can fight back against cancer. These T-cells typically target different receptors that cancer cells use. Cancer has methods of getting around this. As an innovator in the first broad-spectrum immunotherapies, it is incredibly important that there are very few limitations. However, this is not the case, and only a few types of cancer are treatable through CAR T-Cell therapy. Other types could, theoretically, be treated by using different receptors. The cost-effectiveness of this expensive immunotherapy is debated, due to its drawbacks.

The first CAR T-Cell therapy was FDA-approved in 2017. Since then, six total therapies have been designed and approved. Recently, researchers have begun testing methods of overcoming the drawbacks that, unfortunately, define this therapy. Solid tumors, which are a major hurdle with most cancer treatment, typically have environments that are too dense and hostile for standard methods to treat. New developments in CAR-T therapy may have found ways to fight tumors directly and could be on the way to solving other major problems.

Introduction

T-cells are harvested from the patient's body using leukapheresis, and in the laboratory, a specific receptor is inserted onto them. This binding point, the chimeric antigen receptor (CAR), binds to antigens on the surface of cancer cells. These modified cells are then cultured in the laboratory until a mass amount of successful CAR T-Cells are available for infusion into the patient. The cancers it can treat are specific, due to the receptor most commonly targeted in the therapy: CD19. The biomarker (antigen) CD19 appears on all B-cells in the body. This biomarker is a major part of B-cell signaling and performs some protein binding [1]. By targeting CD19, CAR-T is able to treat cancer that involves B-cells, such as certain types of lymphoma and leukemia. This synthetic biology is similar to how the body naturally treats cancer but is custom engineered for a high success rate. CD19-negative cancers are not treatable using this form of CAR-T – which rules out the majority of human cancer.

A major worry of immunotherapy is the possible effects that will come from treatment, especially negative ones. Survival rates, post-treatment outlook, and symptoms of treatment are highly important statistics for patients to know. Of the more dreaded side effects, Cytokine Release Syndrome (CRS) is one of the top reasons that patients decide not to opt into immunotherapies like CAR-T. Cytokines are proteins released by T-cells during cancer treatment – they act as cell messengers that help guide immune response. When there are large amounts of cytokines in the body, inflammation and interruption of bodily processes can occur. In severe cases, this can ultimately lead to organ failure and death. Prevention of CRS is possible, but whether a person develops it is a coin flip – some bodies will respond to cancer aggressively, some will not. Luckily, most patients recover from CRS in 1-2 weeks with no lasting damage.

Due to the amount of customization and behind-the-scenes work of this immunotherapy, it comes with a high price tag [3]. Each infusion is worth between $373,000 and $475,000, excluding the cost of extra procedures and facility for the patient (which adds around $80,000). Even if the

patient is able to cover the costs of the treatment, the side effects, like CRS, may not be worth it. Estimates show that around 80% of patients who take CAR-T therapy achieve remission after a single infusion. Though the price, literal and metaphorical, is high, the statistics continue to bring patients to this therapy.

Recent Progress in CAR T-Cell Therapy

Due to the limitations of T-cell therapy, research and trial is very necessary. There are many facets that can be improved on and tested, though there are very few active trials at any given moment.

Recently, two major research projects have yielded incredible results within this therapy. Both of these showed the ability to shrink solid tumors in mice, which is a massive step for cancer research. The first team developed CAR T-cells which can produce 'fuel' after contacting a tumor [2]. These cells were created with an extra binding site, which produces the cytokine IL-2 upon contact with tumor cells. Early studies using IL-2 were riddled with the extremely toxic side effect, cytokine release syndrome (CRS), but later studies partially remedied this with minor tweaks to the system used.

The second team created CAR T-Cells with cellular functions that can be turned off and on [2]. They built a system of synthetic gene regulators, which could be turned off and on over time. These regulators would be likely controlled with the presence of safe cancer drugs. Giving the CAR T-Cells the ability to 'turn off' may help solve the issue of T-cell exhaustion and could boost overall immune response. T-cell exhaustion occurs when a T-cell loses its ability to kill diseased cells, typically when the immune system has been active for an extended amount of time. This phenomenon is a driving factor in cancer treatment – the longer the body is sick, the more T-cells will eventually become exhausted and lose their ability to fight the cancer. This research also suggested that T-cell exhaustion is reversible, even in the most fatigued cells.

A third research group proposes using CD19-fusion proteins [1] to target alternative tumor antigens in cancers that are CD19-negative. The difficulty lies with determining which antigens to target – this group shows progress with HER2-positive (a growth protein) tumor cells, and suggests that any tumor antigen could be targeted. Predictive CAR-T products [3] are a very recent development – this is a mathematical approach to the microbiologic mechanisms by which CAR-T therapy is defined. A group of researchers laid out a model that can accurately predict the outcome of a patient's biological interactions.

Closing Discussion

Much progress can be expected from this immunotherapy. Though the field of cancer research is vast, few research teams have made much progress with CAR-T therapy. In much immunotherapy research, the difficulty lies with obtaining funding and the source material – immune cells, test animals, cancerous cells, proper equipment, etc. Comparative research is extremely lacking. Because this therapy is quite new, this is to be expected – however, due to the price tag and side effects, many argue whether the therapy is worth research at all.

There remain many unanswered questions from the public. What kind of side effects do these new studies report? How much research is ongoing? Will a certain type of cancer have more side effects with the therapy than another type? How valid are these one-off studies? How much more progress will there be with CAR T-Cell therapy? Most applications that eligible patients need

have either not been researched thoroughly, or do not exist yet. Further customization for T-cell therapy is predicted to be available with more testing. Many of these advancements will take years of study – and many cancer patients do not have years.

References

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