The Use of Immunotherapy to Treat T-cell Acute Lymphocytic Leukemia

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Cancer is characterized by uncontrollable cell growth in the body, often leading to the formation of tumors that can spread to other parts of the body. The immune system is a network of organs, white blood cells, and proteins that protect the body against illness and infection. It is composed of two main parts: the innate and adaptive immune systems. The innate immune system is the body's first line of defense, but is limited in its ability. The adaptive immune system responds slower than the innate immune system, but it has the unique ability to remember germs, and target specific germs ("The innate and adaptive immune systems" 2020). Nevertheless, cancer has ways to evade the body's immune system. It has the ability to downregulate MHC so that T cells are unable to recognize the cell as harmful. It can also block costimulation in T cells using CTLA-4, causing the cells to undergo apoptosis, or upregulate immune checkpoints to turn T cells off. Additionally, when a cancer cell contains tumor associated antigens, there is generally tolerance to those antigens because if the immune system were to attack those antigens, it would also damage healthy cells. Immunotherapy is a type of biological therapy that helps the immune system fight cancer using several different techniques ("Immunotherapy for cancer" 2019). In this review, we discuss how monoclonal antibodies and chimeric antigen receptors can be used to treat T-cell acute lymphocytic leukemia, and how the advancements of these techniques can potentially increase survival rates and efficiently treat patients diagnosed with the cancer.

T-cell acute lymphocytic leukemia, also known as T-ALL, is a common type of cancer of the blood and bone marrow, which is the spongy tissue inside bones where blood cells are made and stored until they are mature enough to enter the bloodstream (Mayo Clinic Staff 2022). It is one of the subtypes of acute lymphocytic leukemia, the other most common one being B-ALL. The word "acute" refers to the rapid progression of the disease, and therefore, the importance of getting immediate treatment after diagnosis. ALL is the result of mutations in the genetic material of the bone marrow, although the exact cause of these mutations is unknown. Typically, a normally functioning DNA contains instructions that inform a cell about when to grow and die; however, mutations may allow the bone marrow cell to continue producing immature blood cells that never mature and allow their growth to become out of control. In T-ALL, immature T cells that the bone marrow produces, called lymphoblasts, never mature into healthy lymphocytes. Instead, the unhealthy cells build up in the bloodstream and other areas of the body, reducing platelets levels and increasing chances of anemia, frequent bleeding, bruising, and fatigue. While there is no current known cause, certain factors are likely to increase the risk of developing T-ALL, including exposure to radiation, and genetic disorders such as Down syndrome. Though one can be diagnosed with T-ALL at any age, individuals younger than fifteen or older than fifty are more likely to develop the disease, with most diagnoses being in young kids from ages two to five. In fact, ALL is the most common cancer found in children, and affects Hispanic children the most. Children are most likely to recover from the cancer with approximately 98 percent of children diagnosed with the disease going into remission and almost 90 percent of individuals younger than fifteen surviving after five years of diagnosis. Survival rates decrease the older the patient is, and only about twenty percent of people over forty will survive after five years of diagnosis. However, survival rates are increasing as treatments improve and advance. Currently, the most common treatment for acute lymphocytic leukemia is chemotherapy, a treatment that has the ability to reach cells all over the body, making it useful for a blood cancer like T-ALL that is spread throughout the body. (American

Cancer Society 2021). Chemotherapy uses the phases of induction, consolidation, delayed intensification, and maintenance to attack the cancer cells. Another common treatment is targeted therapy which can be more useful in targeting and destroying cancer cells for certain individuals. Immunotherapy can also be used to treat T-ALL, and it offers two primary approaches: monoclonal antibodies and chimeric antigen receptors (Caracciolo 2023).

Recent advances in immunotherapy, prominently featuring monoclonal antibodies (mAbs) and chimeric antigen receptors (CARs), have shown promise in treating relapsing patients suffering from cancers, including T-ALL. However, a major setback is that these immunotherapies may also harm healthy T cells due to the shared expression of targeted antigens among both healthy and malignant T cell populations. Currently, chemotherapy is the main treatment for T-ALL and it has increased survival rates to above 85% (Caracciolo 2023). Nevertheless, relapse rates are still high, especially in adults, with over 30% of adult T-ALL patients experiencing relapse within 7-22 months of remission, and less than 10% of the relapse patients surviving. There are few drugs or therapies available for those that have relapsed, and the development of immunotherapies is a crucial step to curing patients with T-ALL. The shared surface markers between healthy and leukemic T cells pose a barrier to targeted T-ALL immunotherapies, causing secondary T-cell immunodeficiency during therapy that could lead to dangerous infections. Overcoming this challenge involves identifying unique markers on T-ALL blasts and creating treatments that selectively target leukemic cells while safeguarding healthy T cells to prevent immunodeficiency complications. Some promising immunotherapy strategies are based on monoclonal antibodies (mAbs) and CARs. MAbs are effective because they have the unique ability to recognize antigens on the surface of the cell, and block them from interacting with other substances, causing the target cells to self-destruct. They also increase cell elimination through antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). ADCC involves mAbs binding to cell antigens, triggering cytotoxic activity in immune cells. This interaction releases granzyme and perforin, causing target cell death. CDC activates the complement cascade after mAb recognition, forming the membrane attack complex (MAC) and causing cell lysis. Another approach to mAB-based immunotherapy relies on antibody-drug conjugates that are made up of mAbs linked to cytotoxic agents that are released in the target cell to trigger apoptosis. Antibodies that are currently going through clinical trials to treat patients with T-ALL include Isatuximab (anti-CD38), Alemtuzumab (anti-CD52), Daratumumab (anti-CD38), and Isatuximab (anti-CD38) (Bayón-Calderón 2020). CAR T-cell therapy is another powerful and effective strategy for fighting cancer, but it has several limitations when it comes to T-ALL. CAR T-cell therapy modifies a patient's T cells *ex vivo* to recognize and attack cancer cells. Extracted T cells are engineered to target specific cancer surface markers, expanded in the lab, and reintroduced into the patient. Upon encountering these markers, the modified cells activate and destroy the cancer cells. As previously stated, CAR T cells and malignant T cells share antigens which can cause self-recognition and lead to CAR T cell fratricide.. Similarly, because cancerous T cells and regular T cells have similar surface protein expression, the on-target/off-tumor cytotoxicity of CAR T-cell therapy can induce a severe T-cell aplasia, causing further health complications (Caracciolo 2023). The first generation of CARs was able to activate and trigger the killing of target cells, but struggled to support the long term growth of CAR T cells. Instead, the clinical application of CARs focuses on second and third generations that provide the crucial signals to activate T cells and make CAR T cells more powerful. Although it is also seen on healthy T cells, CD5 is a surface marker that is frequently seen on cancerous T cells. By controlling T-cell

activity, it avoids an excessive response against the body's own cells. For these tumors, researchers are looking into CAR T-cell therapy that targets CD5. In clinical studies, antibodies that target CD5 in T-cell cancers showed potential without having serious adverse effects. Due to CD5 inducing CAR T-cell fratricide, or self-destruction, certain issues emerged. One method was to use a safety switch to turn off the CAR T cells as necessary. Other approaches are also being explored, such as the use of NK cells or gene editing to produce CD5-negative T cells for CAR modification. Another target for CAR T-cell therapy is CD7, a protein expressed in over 95 percent of T cell leukemias. The partial downregulation of CD7 can also result in the self-destruction of healthy cells, posing difficulties for the use of CD7 in CAR T-cell therapy. In order to address this, techniques such as gene editing and CD7 surface expression blocking allowed CAR T-cell proliferation without the need for self-targeting. While still in its early stages, preclinical research for both CAR T-cell therapies and monoclonal antibodies exhibit the possibility of advancing and improving treatments for T-ALL (Bayón-Calderón 2020).

An ongoing phase 1 clinical trial aims to evaluate the safety of SENL101, an anti-CD7 CAR-T therapy, in patients with relapsed or refractory T-LBL/ALL (NCT06136364). Individuals eligible for the treatment need have either experienced a relapse with primordial cells appearing again in the peripheral blood or bone marrow, or had to have failed to achieve complete remission after receiving at least two cycles of a standard induction treatment regimen. Additionally, they need to have CD7+ tumor cells detected in their body, with $CD4^{-}CD8^{-}$ double-negative cells if found in peripheral blood. They must also have a life expectancy exceeding 12 weeks and be between the ages of 18-75. Individuals are ineligible to join the cohort if they have a history of hematopoietic stem cell transportation, have malignancies other than T-cell acute lymphoblastic leukemia/ lymphoma, have a history of seizures or strokes, have a history of autoimmune diseases, or a form of heart disease.. A second clinical trial in, also phase 1, is studying the safety and feasibility of a combination of different immunotherapies to treat T-ALL (NCT05277753). It utilizes multi-antigen-targeted CAR-T cells, engineered immune effector cytotoxic T cells, and immune modified dendritic cell vaccine. In order to participate in the study, patients must be older than 6 months, have a bone marrow sample with over 30 percent of blast cells, and have adequate bone marrow, liver, and kidney functions. They must also express the proteins CD7, CD5, CD317, CD47, CD99, CD38 or TRBC1/2, in cancerous T cells. Individuals with bacterial or viral infections, HIV, HBV, or other medical conditions are excluded from participating. Furthermore, pregnant or nursing women may also not participate. As both studies are still in their early stages, and are testing relatively new treatments, conclusive results regarding the effectiveness of the treatment are yet to be obtained (Cheng 2023).

T-cell acute lymphocytic leukemia is a blood cancer that typically originates in the bone marrow as a result of the overproduction of immature T-cell lymphoblasts. Although different immunotherapies, particularly monoclonal antibodies and CAR T-cell therapy, have shown promise in preclinical studies and research, their effectiveness varies when it comes to treating the disease. The main challenge researches encountered while studying immunotherapy is the shared antigens between deficient and normal T-cells, resulting in the fratricide of healthy cells. Currently, scientists are working on advancing immunotherapies for T-ALL by identifying surface markers unique to T-ALL cells and mitigating off-target effects to improve the safety of the treatment. With new advancements and continued clinical research, immunotherapy has the potential to provide targeted treatments that are effective in increasing survival rates, and

decreasing relapse rates of patients diagnosed with T-ALL, forever changing the landscape of T-ALL treatment (Bayón-Calderón 2020).

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