Use of CAR T-Cell Immunotherapy in Acute Lymphoblastic Leukemia:

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Introduction

Acute lymphoblastic leukemia (ALL) is a cancer of the white blood cells that starts in the bone marrow. The immune system is the body's defense network that identifies and destroys harmful invaders like viruses, bacteria, and abnormal cells. Normally, it should recognize cancer cells as abnormal and eliminate them before they grow and spread to other organs. Immunotherapy is a treatment that helps the immune system work better to find and attack cancer cells. ALL, the most common childhood cancer affecting nearly 3,000 children annually in the US, has been revolutionized by CAR T-cell immunotherapy, offering new hope for treatment resistant cases. ALL is a type of blood cancer that targets the white blood cells called lymphocytes. It is characterized by the rapid production of immature, abnormal lymphocytes that displace healthy blood cells in the bone marrow. Lymphocytes are types of white blood cells essential to the immune system, responsible for fighting infections and cancer. The bone marrow holds these white blood cells along with red blood cells and platelets. ALL usually affects early forms of B cells or T cells. In B cell ALL, the leukemia cells grow out of control and crowd out the normal blood cells. These cancer cells can also hide from the immune system, which lets the disease keep growing.. They do this by changing the proteins on their surface that the immune system usually recognizes. They also release signals called cytokines that suppress immune activity and attract cells that weaken the body's immune response, such as regulatory T cells and myeloid-derived suppressor cells. In addition, the immune cells that should fight leukemia, especially cytotoxic T cells, often become exhausted and stop working properly. This review paper will cover how the use of immunotherapy, specifically CAR T-Cell therapy, can treat this cancer by working with the immune system against the cancerous cells and its current limitations and future innovations.

Overview of Acute Lymphoblastic Leukemia

The exact cause of ALL is still unknown. However, there are risk factors that can increase chances of developing it. These include certain genetic mutations, specifically those on chromosomes 9 and 22, and history of family members with the disease. In addition, there are environmental factors such as exposure to radiation, benzene exposure, and some chemotherapy drugs. There are also viral triggers such as Epstein-Barr virus (EBV) and Human T-cell leukemia virus-1 (HTLV-1).

ALL mostly affects children but can also occur in adults, especially those over 50. Demographic factors influence risk and outcomes, including age, race, and sex. ALL is the most common cancer in children, with the highest risk for those under 5 years of age. Children generally have a better prognosis and a higher chance at being cured than adults. While 9 out of 10 children with ALL survive, only about 4 out of 10 adults do, making early detection in children especially important. ALL is less common in adults, with approximately 20–25% of all ALL cases being diagnosed in adults. To add on, white and hispanic/latino children have a higher risk of ALL than African American children. The incidence rate is highest in Hispanic/Latino people across all age groups. Research suggests that some of these differences can be linked to genetic mutations. This is helpful for treatments like immunotherapy that target gene mutations to fight cancer. One specific gene variant, the IKZF1 gene, associated with childhood ALL is more common in Latino and East Asian children than in those of European or African ancestry.

Also, the risk of developing ALL is slightly higher in males than in females. The difference is more obvious for the T-cell subtype of ALL.

A variety of underlying genetic mutations, including chromosomal rearrangements and deletions affect the development of ALL. One mutation linked to this disease is a mutation in the Philadelphia chromosome, which is a translocation between chromosome 9 and 22. Furthermore, there are mutations like ETV6-RUNX1 (TEL-AML1), JAK1 mutations and NOTCH1 mutations that are associated with ALL. People with ALL usually have very high survival rates as children, often going past 90% for 5-year survival, but adult survival rates are significantly lower, with the 5-year survival rate being around 40-50%, though this can vary by age. Age and other risk factors affect these statistics.

Patients with ALL are primarily treated with chemotherapy, usually in multiple phases: induction, consolidation, and maintenance. Other treatments include targeted therapy. For example, immunotherapy such as CAR T-cell therapy. This type of therapy uses the body's immune system, with agents like CAR T-cells, to fight the cancer. Doctors use CAR T-cell therapy to treat certain patients with relapsed or refractory (cancer that hasn't responded to other treatments) ALL. It's an option for children and young adults. In addition, radiation therapy (especially in cases involving the central nervous system), and in some high-risk cases, a stem cell transplant are used for treatment of the disease. In conclusion, the fast growing blood cancer ALL shows promising outcomes with CAR T-cell immunotherapy, which has the potential to save lives and even cure many pediatric patients.

CAR T-Cell Therapy in ALL

One of the most important accomplishments for relapsed or difficult B-cell ALL is CAR T-cell therapy. This is a type of immunotherapy that uses the patient’s own immune cells to find and kill leukemia cells. In this treatment, doctors collect T cells from the patient’s blood and send them to a lab. There, the T cells are genetically modified to make a receptor called a CAR (chimeric antigen receptor). This receptor helps the T cells recognize and attack a specific protein on leukemia cells, usually CD19, which is found on most B-cell leukemias. After the T cells are modified and multiplied, they are infused back into the patient, where they search for and destroy the cancer cells that carry CD19.

CAR T-cell therapy mainly targets the leukemia cells, but it depends on the patient’s T cells, both CD4 helper and CD8 killer T cells, to do the work of killing the cancer. The most well-known FDA-approved CAR T therapies for B-cell ALL are Kymriah (tisagenlecleucel), approved for children and young adults, and Tecartus (brexucabtagene autoleucel), approved for adults with relapsed or refractory ALL. In clinical trials like the ELIANA study, CAR T therapy led to remission rates around 80% in patients whose leukemia had come back multiple times, showing that it can be very effective when all other treatments fail. In the trial, a small fraction of patients remained disease free at year one and even past that. Often about 50% or more by year two or three remained disease free, and a minority, about 44%, of patients are still relapse free five years later, suggesting long term remissions and highlighting the potential of this treatment.

However, CAR T-cell therapy also has challenges and limitations. One major problem is cytokine release syndrome (CRS), a dangerous immune reaction that causes fever, low blood pressure, and breathing problems. Another possible side effect is neurotoxicity, which can cause confusion, seizures, or swelling in the brain. Doctors can usually manage these side effects in the hospital, but they can still be life-threatening. Some patients also relapse after treatment

because their leukemia cells lose the CD19 protein or switch to a different cell type that the CAR T cells can't recognize. Leukemia cells can lose CD19 by mutating the CD19 gene, changing how the protein is made, or downregulating it so it does not appear on the cell surface anymore. They may also undergo lineage switching to a non–B-cell type, allowing them to escape CD19-targeted therapies like CAR T-cells.Additionally, creating the CAR T-cells takes time and is very expensive, making it hard for some patients to access this therapy.

Even with these limitations, CAR T-cell therapy has transformed the outlook for people with ALL, especially those with few options. Researchers are now working on improving this treatment by creating CAR T-cells from donors, targeting multiple antigens at once to prevent relapse, and developing new CAR designs that last longer and cause fewer side effects.
In conclusion, CAR T-cell therapy works by reprogramming a patient's own T cells to attack leukemia cells that the immune system normally can't detect. It has shown amazing success in achieving remission for many patients with relapsed or refractory ALL, but it still faces challenges with toxicity, relapse, and cost. Despite these issues, the FDA-approved therapies Kymriah and Tecartus mark major accomplishments in using the immune system to fight cancer.

Innovation and Future Direction: Clinical Trials

Two ongoing clinical trials are exploring innovative uses of CAR T-cell therapy to improve outcomes in patients with ALL, specifically addressing the challenges of relapse and treatment resistance that limit other kinds of immunotherapy. The first trial, NCT06752785, is a Phase 1 study designed for children aged 1 to 18 years with minimal residual disease (MRD), positive B-lineage ALL following induction chemotherapy. Eligible participants must have leukemia cells expressing CD19 and/or CD22, remain MRD-positive on day 46 of induction, and weigh at least 10 kg. Exclusion criteria include active central nervous system leukemia, concurrent malignancies, uncontrolled infections, or viral infections such as HIV, HBV, or HCV. The trial tests a dual-target CAR T-cell product engineered to express receptors for both CD19 and CD22 antigens. This dual targeting is designed to overcome a major immune evasion mechanism, antigen loss, which occurs when leukemia cells stop expressing CD19 to escape recognition by CD19 specific CAR T-cells. Prior studies with CD19 only CAR-T therapies have shown strong initial remission rates but limited durability due to CD19 negative relapse. By simultaneously targeting CD19 and CD22, this trial is aiming to enhance immune security, reduce the risk of relapse, and improve long term remission rates in pediatric patients who still have the disease after chemotherapy. Participants receive lymphodepleting chemotherapy with fludarabine and cyclophosphamide before CAR-T cell treatment, following a treatment sequence proven to promote CAR-T expansion and persistence.

The second study, NCT07072494, is a Phase 1/2 trial enrolling teenagers and adults aged 14 to 80 years with B-cell ALL who are either newly diagnosed or relapsed/refractory but have achieved complete remission following chemotherapy or immunotherapy. Importantly, these patients are ineligible for allogeneic hematopoietic stem cell transplantation (HSCT) due to age, comorbidities, or other risk factors. To qualify, participants' leukemia cells must express CD19, and they must have fewer than 5% blasts in their bone marrow at enrollment. Exclusion criteria include previous CAR-T therapy, mixed-phenotype or biphenotypic leukemia, uncontrolled infection, and significant organ dysfunction. The therapy being tested involves a CD19 directed CAR-T cell infusion at a dose of approximately $0.25–0.5\times10^{8}$ live cells following lymphodepleting chemotherapy. Unlike earlier studies that used CAR-T therapy as a life line treatment for relapsed or refractory disease, this trial introduces CAR-T therapy as a

consolidation strategy, administered when patients are already in remission. Treating patients while they are in remission is often more effective because the cancer level is lower, making it easier for therapies like CAR T-cells to eliminate remaining disease. Waiting for relapse allows the cancer to grow and develop resistance, making treatment harder and less successful. This approach aims to extend remission, reduce the risk of relapse, and offer a potentially curative alternative for patients who cannot get a HSCT, the current standard therapy. The immune evasion mechanism targeted here is the persistence of residual CD19 positive leukemic cells that can later drive recurrence. By administering CAR T-cells at an early disease stage, the therapy may eliminate these malignancies before they evolve immune escape mutations.

Together, these trials represent the next generation of CAR-T immunotherapy in ALL, each tackling a different limitation of earlier treatments. The pediatric CD19/CD22 dual-target trial (NCT06752785) aims to prevent antigen-loss relapse, while the teenager and adult CD19 CAR-T consolidation trial (NCT07072494) seeks to extend CAR-T access to transplant ineligible patients and move therapy earlier in the treatment plan. Both studies use improved safety monitoring, refined dosing, and enhanced cell manufacturing protocols to minimize cytokine release syndrome and neurotoxicity, common side effects of CAR-T therapy. By addressing the biological barriers of early CAR-T therapies, these trials have the potential to make sustaining remission achievable across larger age ranges and disease stages in ALL.

Conclusion

ALL, an aggressive cancer of the bone marrow and blood that causes the body to produce large numbers of immature lymphocytes, a white blood cell, crowds out normal blood cells and impairs immune function. It is most common in children but can also affect adults, often leading to symptoms such as fatigue, infections, and easy bleeding. ALL is one of the best examples of how effective immunotherapy can be in cancer treatment. This success is mainly because ALL cells express clear antigens like CD19 or CD22 on their surface, allowing engineered T cells to specifically recognize and eliminate the cancer without attacking most healthy tissues. However, while initial responses are strong, some patients relapse due to loss of target antigens or limited persistence of the CAR T-cells, making continued research important. Patients relapse because their leukemia cells lose the target antigen CD19 or because the infused CAR T-cells do not persist long enough to provide lasting protection. This highlights the need for ongoing research to enhance CAR T-cell strength, prevent antigen escape, and develop strategies to improve long term outcomes. The main immunotherapies for ALL include CAR T-cell therapy and monoclonal antibodies (like blinatumomab). CAR T-cell therapy has produced amazing remission rates, even in relapsed or treatment-resistant patients. Researchers are developing next generation CAR T-cells to reduce relapse, prevent immune escape, and minimize toxicities such as cytokine release syndrome, as well as expanding therapy access and durability. In the future, immunotherapy could make long term, chemotherapy free, remission possible for most ALL patients, potentially transforming it from a life threatening disease into a curable or chronically manageable condition.

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