Utilizing Immunotherapy for the Treatment of Chronic Lymphocytic Leukemia

Areepitak, R., Pearson, AN.

Introduction

Cancer is a group of diseases characterized by uncontrollable cell growth and the spread of abnormal cells that can invade and damage surrounding tissues and organs. These uncontrolled cells often lead to the formation of tumors and spread to other parts of the body through the blood and lymphatic systems. The immune system is a network of cells, tissues, and organs that work together to eliminate pathogens once they enter the body. This system performs its functions with both innate and adaptive immunity. The immune system also plays a crucial role in maintaining homeostasis and repairing damaged tissues. The immune system should be able to identify cancerous cells and present cancer-specific antigens to T cells. Cancer cells avoid these mechanisms by altering antigen presentation, suppressing immune responses, and changing the signaling pathways involved in immune responses. Immunotherapy is a type of medical treatment that enhances or stimulates the immune system to acquire an improved ability to recognize and destroy cancerous or any abnormal cells. Immunotherapy is an attractive option to overcome cancer immune evasion because it offers targeted and specific approaches as well as overcoming tolerance by blocking immune checkpoint proteins. In this review, we will talk about the different types of immunotherapy being used on Chronic Lymphocytic Leukemia.

Immunotherapy on Chronic Lymphocytic Leukemia

Chronic Lymphocytic Leukemia (CLL) is a complex hematologic malignancy that involves various genetic, immunologic, and clinical factors, making its diagnosis and treatment challenging. To diagnose this disease, blood tests are used to count B cells and assess lymphocyte types. A test called fluorescence in situ hybridization (FISH) examines chromosomes in cancerous lymphocytes for genetic changes by visualizing target DNA sequences of mRNA in metaphase or interphase cells and tissue sections. Doctors are not yet certain of what triggers CLL, but it occurs with genetic changes in bone marrow cells that lead to rapid production of B lymphocytes. The changes also cause the blood cells to produce abnormal, ineffective lymphocytes. Then, the mature B lymphocytes accumulate in the peripheral blood, bone marrow, and secondary lymphoid organs, killing the healthy lymphocytes as they continue to multiply. Monoclonal B cell lymphocytosis (MBL) causes an increase in abnormal lymphocytes to build up. Unfortunately, numerous individuals afflicted with this disease will initially exhibit no symptoms, as it progresses insidiously and gradually worsens over time. CLL may cause swollen lymph glands or abdominal discomfort from an enlarged spleen, weight loss, infections that won’t get better, bone pain, night sweats, and the feeling of fatigue. CLL occurs most often in older adults, typically 65 years or older. People of European descent are also more likely to develop this disease (Meissner 2020). According to the National Cancer Institute, roughly 90% of cases occur in white males (Meissner 2020). The rate of CLL is 6.3 per 100,000 males and 3.3 per 100,000 females. Certain herbicides and insecticides, including Agent Orange used during the Vietnam War, have been linked to an increased risk to this disease, as well as radiation exposure, tobacco smoke, blood disorders, and Down Syndrome. Australia and New Zealand have the highest CLL incidence rate. The most common genetic

abnormality in CLL are the deletions of chromosome 13. Approximately 80% of CLL patients carry at least 1 of 4 common chromosomal alterations, namely deletion 13q14. The lifespan of people who have this disease varies from person to person. Some patients pass away within several years of diagnosis, but most people have an 88% 5-year survival rate. Some patients have an indolent leukemia, while others experience an aggressive disease, with early and frequent need of treatment. Patients are usually treated with chemotherapy, immunotherapy, and a bone marrow transplant (BMT), also known as a stem cell transplant, which uses strong chemotherapy drugs to kill the stem cells in the bone marrow that are creating diseased lymphocytes. Then, adult blood stem cells from a donor are infused into the blood, where they travel to the bone marrow and begin making healthy blood cells. BMT safely allows treatment with high doses of chemotherapy or radiation by replacing or rescuing the bone marrow damaged by the treatment. Doctors would only likely suggest a transplant if the patient is young and healthy enough to withstand intensive treatment. As new and more effective drug combinations are being developed, bone marrow transplants have become less common in treating CLL. Patients are also treated with targeted drug therapy with drugs such as Ibrutinib, a Bruton tyrosine kinase (BTK) inhibitor, which inhibits BTK, a critical kinase and protein for CLL development and expansion.

Immune dysregulation is a cardinal feature of chronic lymphocytic leukemia (CLL) from its early stage. The CLL tumor evades the immune system by directly suppressing the natural function of cells. Studies have documented that CLL cells impacts T cells and B cells by direct cell contact and the release of tumor derived soluble factors, interacting with T cells and B cells through surface molecules that send inhibitory signals and secrete cytokines and other soluble factors that create an immunosuppressive microenvironment. Tumor cells inhibit the effector arm of the immune system, by expressing various inhibitory surface molecules, such as PD-L1, that bind to receptors on effector immune cells (e.g., PD-1 on T cells), leading to their inactivation. CLL tumor cells typically downregulate Human Leukocyte Antigen class I (HLA-I) to evade the T cell immune response through genetic, epigenetic, transcriptional, and post-translational mechanisms, and compense NK cell cytotoxicity, therefore they become most dysregulated when evaded. Multiple inhibitory functions of HLA-G, an additional mechanism through which tumor cells escape the immune response through an antigen, were described against NK cells, T lymphocytes, and Antigen-Presenting Cells (APCs) by directly binding to their inhibitory receptors ILT-2, ILT-4, and KIR2DL4. Monoclonal antibodies and Chimeric antigen receptor (CAR-T) cell therapy are the types of immunotherapy that are used for treating CLL. Monoclonal antibodies, engineered to target Tumor-Specific Antigens (TSAs), are widely recognized in CLL immunotherapy. These antibodies primarily target B cells by binding to markers like CD20, CD19, and CD37. These antibodies have a fixed region that helps monocytes bind to CD20, CD19, CD37 and a variable region that recognizes the cancer cell marker. The antibodies work by marking cancer cells for destruction by the immune system through processes like antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADP). Over the past 20 years, the effects of Linalidomide, an immunomodulatory drug (IMiD), have become significantly better understood and widely acknowledged. The main limitation in using immunotherapy, such as CAR-T cells for CLL, is that T cells often have inherent issues that affect their growth and function. CAR-T cells from patients who responded well to treatment had higher levels of memory-related genes, boosting their ability to produce cytokines and mount effective immune responses (Fraietta J. A.

2016). On the other hand, non-responders of the treatment CAR-T cells resulted in effector differentiation, glycolysis, exhaustion, and apoptosis. Immunochemotherapy is recommended for younger patients with newly diagnosed IGHV-mutated CLL but not for those without the IGHV mutation. On November 13, 2013, the FDA granted accelerated approval to ibrutinib, a type of cancer growth inhibitor for immunotherapy called a tyrosine kinase inhibitor, for the treatments of patients with Mantle Cell Lymphoma (MCL) and patients with CLL. Ibrutinib received all four expedited programs of the FDA, and the approvals were based on an overall response rate.

A Phase I/II Study of Xcellerated T Cells in Patients With Chronic Lymphocytic Leukemia (CLL) is an ongoing clinical trial that studies the Adoptive Cell Transfer (ACT) for this disease. Patients will receive one dose of Xcellerated T cells(™), an *ex vivo* activated and expanded autologous T cell product, in an attempt to enhance the anti-tumor immune response (NCT00058656). The goal of this study is to determine the safety and the potential efficacy of this treatment. Examples of characteristics in the inclusion criteria include patients with an active intermediate or high risk of CLL defined by the modified 3-stage system, a life expectancy of six months, and the patients' T cells (CD3+) comprises >1.5% and < 10% of peripheral white blood cells as assessed by flow cytometry. The patients also need to have symptoms associated with the disease, such as weight loss > 10% within the previous 6 months and fevers of greater than 100.5 degrees Fahrenheit for more than two weeks. Examples of exclusion criteria in this CLL clinical trial include evidence of Richter's Syndrome, T cell CLL, prolymphocytic leukemia, hairy-cell leukemia, splenic lymphoma with villous lymphocytes, large granular lymphocytosis, Sezary-cell leukemia, or leukemic manifestations of non-Hodgkin's lymphoma. Overall, this research aims to evaluate the safety and establish the maximum tolerated dose (MTD) of Xcellerated T Cells in patients with CLL. Changes in the diversity of T cells and their ability to combat tumors will also be evaluated. The therapeutic effect will be preliminarily evaluated by accessing lymphocyte counts, lymph node area, and quantitative immunoglobulin levels. This study is testing a new dosing strategy with new autologous T cell products while only using one dose (NCT00058656). Xcellerated T Cells are engineered to specifically target CLL cells, so this method of treatment is more specific than the traditional treatment of care in CLL as well as boosting the body's immune system more effectively. Another ongoing trial that involves immunotherapy in CLL is a Phase II study of Ibrutinib, Fludarabine, and Pembrolizumab in high risk or relapsed/refractory in this disease. The goal of this study is to achieve a greater reduction in CLL cells with multiple agents rather than only a single agent, ibrutinib, and to restore a healthier immune system by investigating the rate of response to ibrutinib and short course fludarabine and pembrolizumab (NCT03204188). Patients who are eligible for the trial are categorized as people with a high-risk of CLL, with a poor clinical outcome when treated with conventional chemotherapy. Some of the inclusion criteria patients have are massive nodes, or progressive lymphadenopathy, and presence of high-risk mutations detected by FISH or targeted sequencing. Patients who cannot participate in this trial have the exclusion criteria, which include a major surgery within 4 weeks of first dose of study drug, or they are currently receiving systemic steroid therapy (i.e. prednisone) or any form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. CLL cells grow and survive because they receive signals through the B cell receptor. Therefore, Ibrutinib inhibits any stimulated B cell

production, which selectively blocks any Bruton's tyrosine kinase (BTK). Despite the use of Ibrutinib being FDA approved, the use of it as a single agent has limitations; the drug does not eliminate all tumor cells and, with time, the tumor cells may become resistant. As a result, combinations of ibrutinib with other drugs are more beneficial (NCT03204188). The use of Ibrutinib, Fludarabine, and Pembrolizumab altogether in immunotherapy enhances the efficacy compared to the standard treatment of care because they can work together to overcome resistance unlike single-agent therapies (NCT03204188). This combination immunotherapy study infers future directions in treating CLL with different types of inhibitors. Based on all the findings, it is more efficient to use multiple drugs instead of single-agent uses and scientists are still trying to find the most useful technique of T cell immunotherapy.

Conclusion

Chronic Lymphocytic Leukemia is a cancer that affects the blood and bone marrow, causing the buildup of abnormal white blood cells. CLL can lead to weakened immune function and other health complications. Immunotherapy for CLL has shown promising results, especially in targeting specific markers on cancer cells. However, the effectiveness can vary depending on individual factors, such as the stage of the disease and specific genetic characteristics. The types of Immunotherapies that are used to treat CLL are CAR-T Cell Therapy, Monoclonal Antibodies, and Checkpoint Inhibitors. CAR-T Cell Therapy has shown significant promise in treating CLL, especially in patients who are resistant to other treatments. Monoclonal Antibodies have been effective in improving remission rates and managing CLL. While still in clinical trials for CLL, Checkpoint Inhibitors have shown efficacy in other cancers and hold potential for CLL treatment. Researchers and clinicians in the field of CLL are currently working on resistance mechanisms, personalized medicine, and more immunotherapy innovations. The main obstacles are disease heterogeneity, making it difficult to develop a one-size-fits-all treatment and new side effects. Overall, the integration of immunotherapy in CLL treatment opens up the potential to more effective, personalized, and durable treatment options, improving outcomes for many patients and providing hope for those with challenging or advanced stages of this disease.

References

1. Forconi, F., & Moss, P. (2015). Perturbation of the normal immune system in patients with CLL. *Blood, The Journal of the American Society of Hematology*, *126*(5), 573-581.

Chicago

2. Arruga, F., Gyau, B. B., Iannello, A., Vitale, N., Vaisitti, T., & Deaglio, S. (2020). Immune response dysfunction in chronic lymphocytic leukemia: dissecting molecular mechanisms and microenvironmental conditions. *International journal of molecular sciences*, *21*(5), 1825.

3. Freeman, C. L., & Gribben, J. G. (2016). Immunotherapy in chronic lymphocytic leukaemia (CLL). *Current hematologic malignancy reports*, *11*, 29-36.

4. Perutelli, F., Jones, R., Griggio, V., Vitale, C., & Coscia, M. (2022). Immunotherapeutic strategies in chronic lymphocytic leukemia: advances and challenges. *Frontiers in Oncology*, *12*, 837531.

5. Robak, P., & Robak, T. (2023). Immunotherapy combinations for chronic lymphocytic leukemia: advantages and disadvantages. *Expert Opinion on Biological Therapy*, *23*(1), 21-35.