The Use of Immunotherapy in Chronic Lymphocytic Leukemia

Shreya Sarangmath, Ashley Pearson

Introduction

Cancer is a disease characterized by cells that proliferate rapidly and irrepressibly, infiltrate tissues, and avoid cell death. The vast array of cancers are classified by mutations and are becoming more prevalent. The immune system includes tissues, cells, and molecules that defend against diseases, illnesses, and infections. There are two main forms of immunity: innate immunity and adaptive immunity. Innate immunity refers to the system that responds rapidly, but with a non-specific response to foreign molecules whereas the adaptive immune system has a delayed but highly specific response. The immune system needs to maintain a balance to where it only responds to threats, and does not have an autoimmune response, in which the system targets itself. In theory, the immune system should be able to prevent progression of cancer. However, due to mutations, and cancer's ability to deregulate T cells, it is able to avoid the immune attack. Immunotherapy is a method of treatment that targets the immune system to respond to cancer, rather than targeting the cancer itself. Immunotherapy can be an attractive option for patients who have previously tried other treatments, or need to enhance the effects of other treatments by pairing them with immunotherapy.

Main Body

Chronic lymphocytic leukemia (CLL) is the most frequently occurring form of leukemia cancer in the Western hemisphere (Hallek, 2019). CLL is typically categorized by developing lymphocytes in the blood, bone marrow or lymphoid tissue (Kipps, 2017). There are B 1 cells, or white blood cells from the immune system which are responsible for creating antibodies which bind to pathogens and viruses, and eliminate them. CLL is the result of a malignancy in the B cell carrying the CD5+ antigen which is known as a mutation in DNA of the bone marrow. These abnormal cells divide rapidly compared to healthy cells, and due to their mutations can outlive healthy cells, avoiding apoptosis. The CLL cells can travel to lymph nodes, the liver, and the spleen and can accumulate there and form masses, causing the lymph nodes to enlarge . They can also overcrowd the healthy blood cells and cause them to rupture. The ruptured blood cells are visible when conducting a blood smear test. The ruptured cells break due to their fragility, indicating a sign of CLL. Blood counts, blood smears, or bone marrow aspirations are methods to diagnose CLL(Hallek, 2019). Clonal evolution in the cancerous cells can produce driver mutations. These subclonal driver mutations are a factor that can cause the cells to rapidly grow, contributing to the pathogenesis (Landau, 2013). The symptoms may be mild in the beginning stages, but they can progress and become more aggressive. Various symptoms may include swollen lymph nodes, fatigue, fever, pain in the joints or bone, easily bleeding, unwarranted weight loss, night sweats, bruising, or frequent infections. There are many potential symptoms; sometimes it is not visible and the tests are indicative of CLL (Hallek, 2019). This disease primarily affects elderly people who are over the age of 65 (Balducci & Dolan, 2015). It is also more common in the West and rare in Asia. People affected by CLL can live up to decades, and many can live close to life expectancy through treatment. However as it primarily affects older individuals, that could impact their life expectancies. Another factor that could impact life expectancies are autoimmune diseases (Hallek, 2019). CLL has an array of various treatments. There is venetoclax, which is an inhibitor with B cell lymphoma paired with

obinutuzumab. Another treatment option is monotherapy which has inhibitors of Bruton tyrosine kinase (BTK) such as acalabrutinib and ibrutinib. Another form of treatment could be chemoimmunotherapy. If the patient can remain 3 years without treatment and then relapses, initial treatment can be used again. However if the patient relapses before the end of that period, they must seek a different option. Mutations such as *del(17p)* or *TP53* mutation have allowed CLL to be resistant to chemotherapy (Hallek & Al-Sawaf, 2021).

Abnormal cells that result from CLL are able to avoid a cytotoxic immune response because they can cause dysfunction in the T cells. The PD-1 protein is a cell receptor which is responsible for decreasing T cell proliferation, cytokine production, and cell survival (Roessner & Seiffert, 2020)l. Dysfunction in this pathway makes it so that the T cells are not cytotoxic to the cancer Immunotherapies aim to activate the T cells so that they can target the CLL cells. Many immunotherapy treatments fall under the categories of monoclonal antibodies or adoptive cell therapies (Freeman & Gribben, 2016). Monoclonal antibodies (MA) can be used to inhibit the abnormal B cell receptor signaling which is allowing the progression of disease. An example of an MA treatment is ibrutinib, which helps to activate T cells. B cells produce BTK which is a signaling protein in the TEC family kinases. Ibrutinib impacts the differentiation of CD4 T cells into T helper cells that favor antitumor immunity. These kinase proteins are able to activate the T cells, promoting proliferation so they can react to the CLL (Mhibik, 2019). Similar monoclonal immunotherapies include rituximab, ofatumumab, and there are several others that all share a similar function of blocking abnormal signals and allowing helper and memory T cells to proliferate. While these treatment options are helpful, the T cells can be disease associated, or the cancer can develop resistance to ibrutinib. For this reason, monoclonal immunotherapies are often administered with another treatment such as chemotherapy, or can be paired with each other. Another flaw to monoclonal antibodies is that the CLL cells can mutate and develop resistance to the antibody, leaving them undetected by the natural killer (NK) cells. (Freeman & Gribben, 2016). Another method of treating CLL through immunotherapy is through adoptive cell therapies. Adoptive cell therapies utilize a patient's cells and infuse them into the bloodstream in order to strengthen the immune response. An example of this used to treat CLL is chimeric antigen receptor T cell (CAR-T) therapy. This therapy targets the dysfunctional CD4+ T cells which allow CELL to proliferate due to them expressing inhibitory receptors such as PD-1, leading to exhaustion and loss of function. CAR-T therapy involves using a protein variant to increase the efficiency of T cells so that they can recognize CLL specific antigens. For example, a protein variant of p53, Δ133p53α, is able to increase anti tumor activity and limit dysfunctions under conditions of high tumor burden, improving cytotoxicity (Roselle, 2024). While adoptive cell therapies such as CAR-T therapy have proven to be very beneficial in activating T cells and increasing proliferation, making them effective, they can be expensive and can take a large amount of time to culture during a critical stage of disease.

There are ongoing clinical trials helping to identify how immunotherapy is used in CLL. One clinical trial, for example, is studying how a combination of ibrutinib, fludarabine, and pembrolizumab can be an effective method to treating CLL. Ibrutinib's purpose is to activate the T cells, fludarabine is used to control immune cells and CLL cells, and Pembrolizumab is used to activate T cells to attack CLL. This is a phase two study in which the treatment is given from cycle-3 to 17 and is continued until the disease progresses or until there are intolerable side effects. Ibrutinib is given until the disease progresses whereas the other two treatments are short courses and are administered in short courses. Fludarabine is given from day one to day five only in cycle 2. Pembrolizumab is given beginning in cycle 1 every three weeks for one year.

This trial studies high risk CLL, meaning it is relapsed or refractory, or it has developed high risk mutations such as deletion of *17p, TP53, and NOTCH1*. The main eligibility criteria is having high risk CLL which is characterized by relapsed or refractory, or having developed mutations. The study is not open to individuals with recent surgeries or treatment, receiving immunosuppressive therapies, autoimmune disease, additional malignancies that require treatment, bleeding disorders, HIV, hepatitis B or hepatitis C infection, active infections, tuberculosis, sensitivity to the drugs used in the trial, a history of stroke or hemorrhage, cardiovascular disease, pregnancy, breastfeeding, or psychiatric illness. CLL cells thrive on receiving signals from the B cell receptor and T cell interactions help them survive as well. Ibrutinib blocks the B cell receptor signals, however, this treatment does not eliminate all the tumor cells and CLL can also gain resistance to it, making ibrutinib a good candidate to combine with other treatments (NCT03204188). Another clinical trial investigates the use of a CAR T therapy of rituximab, fludarabine, and cyclophosphamide in patients with CLL and SLL. This is a phase two trial looking at an anti CD19 CAR T cell therapy. Treatment involves extracting blood from the patient and separating the T cells which are modified by the researchers and returned to the patient. Phase one of the trial tested safety and phase two tested the overall response rate. To be eligible for this treatment, the patient must be over 18, have a blood malignancy measured by CT scan, at least 14 days between the time of any prior systemic treatment, and uniform CD19 expression. Patients are excluded if they have active infections including hepatitis B or C, or have had prior CAR T therapy. Following treatment, patients must be hospitalized to monitor toxicity and follow up appointments are done from 2 weeks to 12 months. There will also be long term follow ups for 15 years after infusion of CAR T. CD19 is a protein frequently expressed by blood cancers. The aim of this treatment is to modify T cells expressing the Hu19-CD828Z CAR to target the CD19 antigen. Limitations of this treatment option include that there are currently no FDA approved CAR T therapies, that CLL's responses to CAR T therapy have been less than in other B cell malignancies, and that normal B cells could be eliminated as CD19 is expressed by them (NCT06364423).

Conclusion

Chronic lymphocytic leukemia is a common form of blood cancer characterized by a B cell malignancy originating in the blood, bone marrow, or lymphoid tissue. There are various forms of immunotherapy available for treating CLL such as monoclonal antibodies or adoptive cell therapies. Treatments such as ibrutinib or CAR T therapy have demonstrated promising results in research and clinical trials, but are usually paired with other treatments due to some of their limitations as they are not effective in combating mutations of the cancer. Scientists in the field are aiming to overcome this resistance to immunotherapy and the long processes that come with cultured treatments. Immunotherapy in CLL, as well as in many other cancers has displayed potential as an effective way of treatment and with further advances in research, clinical trials, and development, has altered the scope of cancer treatment.

References

Hallek M. (2019). Chronic lymphocytic leukemia: 2020 update on diagnosis, risk stratification and treatment. *American journal of hematology*, *94*(11), 1266–1287. https://doi.org/10.1002/ajh.25595

Kipps, T. J., Stevenson, F. K., Wu, C. J., Croce, C. M., Packham, G., Wierda, W. G., O'Brien, S., Gribben, J., & Rai, K. (2017). Chronic lymphocytic leukemia. *Nature reviews. Disease primers*, *3*, 16096. https://doi.org/10.1038/nrdp.2016.96

Balducci, L., & Dolan, D. (2015). Chronic Lymphocytic Leukemia in the Elderly: Epidemiology and Proposed Patient-Related Approach. *Cancer control : journal of the Moffitt Cancer Center*, *22*(4 Suppl), 3–6. https://doi.org/10.1177/107327481502204s02

Hallek, M., & Al-Sawaf, O. (2021). Chronic lymphocytic leukemia: 2022 update on diagnostic and therapeutic procedures. *American journal of hematology*, *96*(12), 1679–1705. https://doi.org/10.1002/ajh.26367

Landau, D. A., Carter, S. L., Stojanov, P., McKenna, A., Stevenson, K., Lawrence, M. S., Sougnez, C., Stewart, C., Sivachenko, A., Wang, L., Wan, Y., Zhang, W., Shukla, S. A., Vartanov, A., Fernandes, S. M., Saksena, G., Cibulskis, K., Tesar, B., Gabriel, S., Hacohen, N., … Wu, C. J. (2013). Evolution and impact of subclonal mutations in chronic lymphocytic leukemia. *Cell*, *152*(4), 714–726. https://doi.org/10.1016/j.cell.2013.01.019

Freeman, C. L., & Gribben, J. G. (2016). Immunotherapy in Chronic Lymphocytic Leukaemia (CLL). *Current hematologic malignancy reports*, *11*(1), 29–36. https://doi.org/10.1007/s11899-015-0295-9

Roselle, C., Horikawa, I., Chen, L., Kelly, A. R., Gonzales, D., Da, T., Wellhausen, N., Rommel, P. C., Baker, D., Suhoski, M., Scholler, J., O'Connor, R. S., Young, R. M., Harris, C. C., & June, C. H. (2024). Enhancing chimeric antigen receptor T cell therapy by modulating the p53 signaling network with Δ133p53α. *Proceedings of the National Academy of Sciences of the United States of America*, *121*(10), e2317735121. https://doi.org/10.1073/pnas.2317735121

Mhibik, M., Wiestner, A., & Sun, C. (2019). Harnessing the Effects of BTKi on T Cells for Effective Immunotherapy against CLL. *International journal of molecular sciences*, *21*(1), 68. https://doi.org/10.3390/ijms21010068

Roessner, P. M., & Seiffert, M. (2020). T-cells in chronic lymphocytic leukemia: Guardians or drivers of disease?. *Leukemia*, *34*(8), 2012–2024. https://doi.org/10.1038/s41375-020-0873-2

NCT03204188

NCT06364423