Immunotherapy Use in the Treatment of ALL

Stoner, J., Pearson, AN.

Introduction

Cancer is a disease characterized by rapid, uncontrolled cell growth. The immune system, by contrast, is a network of organs, cells, and signaling molecules that serve as a defense mechanism against infections and diseases. The immune system should eliminate cancer; however, there are several immune evasion mechanisms that cancer cells use in order to disrupt or prevent this immune response. Therefore, outside treatment is needed in order to eradicate the cancerous cells. Many traditional treatments directly attack cancerous cells to achieve this goal; however, over the past few decades, a new approach known as immunotherapy has begun to be implemented instead. In immunotherapy, a patient's own immune system is used in order to more effectively attack and eliminate cancer. Immunotherapy is both a promising and attractive treatment option because it allows for highly specialized, antigen specific treatment that is effective without many of the toxicities and side effects that traditional chemotherapy causes. In this review, we will describe the use of immunotherapy in the treatment of acute lymphocytic leukemia (ALL).

Overview of ALL

ALL is the overall most common malignancy in childhood (Chan 2023). It is defined as a malignancy of B or T lymphoblasts, and is characterized by the uncontrolled and continual development of immature, abnormal lymphoid organs. ALL occurs when damage to DNA causes the lymph cells to uncontrollably grow and spread. There are several risk factors that can increase the chances of this occurring, including exposure to benzene and ionizing radiation, previous radiation or chemotherapy treatment, and various genetic diseases such as Trisomy 21, Bloom syndrome, neurofibromatosis type 1, and ataxia telangiectasia. As stated above, ALL most commonly occurs in children, with the peak age of diagnosis being between the ages of two and ten. However, ALL can occur in adults and those over 60 as well. It affects slightly more males than females, and Caucasians about three times as much as African Americans. Symptoms can include anemia, difficulty breathing, a low platelet and neutrophils count, an enlarged liver or spleen, fatigue and weakness, easy bruising or bleeding, abnormal lymph nodes, and cranial neuropathies. Those with a malignancy of the B lymphoblasts also commonly experience frequent fevers, night sweats, and unexplained weight loss (Chan 2023). Treatment of ALL typically takes two to three years and consists of an intensive regimen of about 15 chemotherapy drugs. Outcomes of this treatment vary greatly by age group, and typically become less positive as the age of the patient increases. For young children, the cure rate is 80 to 90%, and for adolescents and young adults, it is slightly lower at 60 to 70%. Adults 40-60 years of age are not far off with a cure rate of 50 to 60%. However, once the age of 60 or older is reached, cure rates decline to 20 to 25%, due to an inability to withstand intensive treatment and increased rates of resistant gene factors (Kantarjian 2021). Even if remission is reached, however, there is still a chance of recurrence up to 20 years after treatment (Chan 2023).

Overview of Immunotherapy use in ALL

Immunotherapy has begun to emerge as a promising new addition to treatment plans for

B-ALL. Immunotherapy uses patients' own immune systems to target cancer and has the potential to increase survival rates while also reducing the toxicity of traditional chemotherapy (Aureli 2023). Thus far, there are three major immunotherapies being used to treat B-ALL: bispecific antibodies (BsAbs), antibody drug conjugates (ADCs), and CAR-T or CAR-NK cells. BsAbs are antibodies that have been engineered to have two different fragment binding antigen regions, which allows for the targeting of two antigens at once. They function to recruit and activate T cells against tumor cells, as well as to enable enhanced T cell activation. In 2014, Blinatumomab became the first bispecific T cell engaging antibody (BiTE) to be approved by the FDA for the treatment of both minimal residual disease (MRD) positive BCP-ALL and relapsed/refractory (R/R) B-ALL in patients of all ages. However, in pediatric patients, Blinatumomab is only recommended for those with R/R Philadelphia chromosome (Ph) negative CD19+ B-cell precursor ALL after 2 prior therapies, relapse after receiving HCT, or high-risk first relapse after consolidation therapy. Blinatumomab specifically works to bind CD19 on B-ALL cells and CD3 on T cells simultaneously, drawing the two cells into close proximity and thus allowing for more rapid and effective tumor killing. Despite its common side effects of cytokine release syndrome (CRS) and neurotoxicity, blinatumomab shows promise of being more effective with less toxicity compared to chemotherapy. When combined with chemotherapy, BsAbs could serve as maintenance therapy or a therapeutic strategy for R/R B-ALL following HCT. Similar to BsAbs, ADCs are also engineered through combining a monoclonal antibody with a cytotoxic drug via various linkers. This allows ADCs to bind to surface antigens on their target, which is CD22 in B-ALL, and then be internalized in order to cause cell death. Through what is known as the bystander killing effect, ADCs can also produce cell death by releasing their cytotoxic drug against the tumor microenvironment in the extracellular space. In 2017, Inotuzumab (InO) was FDA approved for use in R/R adult B-ALL patients. InO shows promise as a treatment option when partnered with low-intensity chemotherapy and with or without blinatumomab, especially for elderly patients who cannot withstand an intense treatment regimen. Even so, it does increase the risk of sinusoidal obstruction syndrome (SOS) when compared with traditional chemotherapy. More promising than both BsAbs and ADCs, however, is Chimeric Antigen Receptor (CAR) engineered immune cell therapy. In this immunotherapy, either T or NK cells are genetically modified with CARs, allowing them to target a specific antigen on tumor cells and combine binding to the antigen and becoming activated into one step. The use of CAR-T cells is currently the most common for this form of therapy. The main target of CAR-T cells is CD19 on B cells, and they may only be used after lymphodepleting chemotherapy has been completed. The FDA approved tisagenlecleucel (CTL019) for R/R B-ALL in 2018 for those up to 25 years of age, as well as brexucabtagene autoleucel (KTE-X19) in 2021 for adults with R/R B-ALL. Side effects of CAR-T cell therapy are severe, including CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), and B cell aplasia related to ICANS. Researchers are working to minimize these side effects, as well as to find new targets such as CD22 or CD20. Some focus has shifted to using NK cells rather than T cells, which have fewer side effects. For CAR-NK cell therapy, NK cells undergo increased activation through blocking inhibitory interactions, expanding NK cell populations, and improving overall functions. Similar to T cells, NK cells work in R/R B-ALL to target CD19. They show promise for targeting CD7 as well. However, unlike T cells, NK cells are much harder to engineer and store for long periods of time. The best gene editing strategies to surpass these issues are still being studied. Overall, new immunotherapies for ALL and the most effective ways to combine them with chemotherapy are still under investigation, especially when it comes to finding effective

immunotherapies for T-ALL (Aureli 2023). New targets for immunotherapy are also being developed, one of which is known as Siglec-15 (Sig15). Sig15 is an immune checkpoint expressed in solid tumor-infiltrating macrophages that has been found to be overexpressed in several blood-related cancers, including B-ALL and T-ALL (Abukharma 2023). It has also been discovered circulating in the plasma of pediatric B-ALL patients in correlation with an immune-suppressive cytokine environment. It binds sialic acid sugar groups on several proteins and can have immune stimulatory or suppressive signaling effects. These effects are suspected to play a role in the suppression of antigen-specific T cell activation. Additionally, Sig15 is known to be able to open a pathway that allows tumor cells to promote TGF-B in nearby tumor-related macrophages. When genetically treated with monoclonal antibodies in mice injected with B-ALL, Sig15 promoted clearance by the immune system by changing the immune environment in the bone marrow to have more early effector CD8+ T cells and less immunosuppressive cytokines. It also caused the production of more CD3+ T cells, NK cells, and neutrophils (Abukharma 2023). As such, Sig15 is one of the most promising emerging targets for immunotherapy in the treatment of ALL.

Innovation and Future Directions

There are many ongoing clinical trials that are focused on the expansion of immunotherapy use in treating ALL. One phase 1 trial is focused on determining the safety, efficacy, and overall feasibility of following multi-antigen targeted CAR-T cells with engineered immune effector cytotoxic T cells (CTLs) and an immune modified dendritic cell vaccine (DCvac) in the treatment of T-ALL (NCT05277753). CTLs are modified to target and destroy a specific antigen on T-ALL tumors, and a DCvac enables dendritic cells to permanently monitor for and dispatch any malignant cells with a specific antigen in order to significantly delay or prevent relapse. The primary desired outcome is NGS MRD negativity in all patients, as persistent MRD levels correlate to a high rate of relapse. The therapies used are designed to augment anti-tumor immunity in order to increase the likelihood of achieving MRD negativity. Participants must be between 6 months and 75 years of age. A bone marrow sample containing at least 30% blast cells for testing purposes, willingness to go through CTL/DCvac preparation, and expression of CD7, CD5, CD317, CD47, CD99, CD38, or TRBC1/2 in malignant cells is required. Specific disqualifiers for this trial include cell separation contraindications and receiving gene therapy at any point or glucocorticoid within one week prior to testing (NCT05277753). This trial addresses the current lack of immunotherapy treatments for T-ALL. If the proposed treatment model is successful in bringing about NGS MRD negativity in most or all patients, then its use could significantly reduce the high rates of relapse associated with T-ALL (Aureli 2023) and thus increase current survival rates. Another similar phase 3 trial is focused on determining if combination therapy with steroids, tyrosine kinase inhibitors (TKIs), and blinatumomab is better than the standard of care for Ph+ B-ALL (NCT04530565). The primary focus is to compare the overall survival (OS) rate when using steroids, TKIs, and blinatumomab with that of using steroids, TKIs, and chemotherapy. Researchers also plan to compare event free survival (EFS) and MRD negativity rates, as well as assess the toxicities associated with both groups. As a final measure, the researchers will record rates of MRD negativity after a second induction and the outcome for patients who proceed to an allogeneic stem cell transplant after steroids, TKIs, and blinatumomab. For this trial, all patients begin in arm A, where they receive steroids and TKIs. They are then randomized into arms B or C. Arm B contains steroids, TKIs, and chemotherapy, while arm C contains steroids, TKIs, chemotherapy,

and blinatumomab. Patients must be between 18-75, have a diagnosis of BCR-ABL1+ and Ph+ B-ALL, and have an Eastern Cooperative Oncology Group (ECOG) performance status between 0-3. No previous chemotherapy for B-ALL is permitted, except for up to 5 days of therapy to reduce disease burden. Total bilirubin must be at or below 3 mg/dL, AST must be no greater than 2.5x the upper limit of normal, and estimated creatinine clearance needs to be above 45 mL/min (NCT04530565). This trial addresses the poor prognosis that Ph+ ALL patients typically receive, in part due to the fact that they are most often older and unable to tolerate high intensity treatments (Wieduwilt 2022). It also addresses the ongoing question of which combination of immunotherapy with chemotherapy is the most effective with the least toxicities, both in the short and long term (Aureli 2023). If the proposed combination therapy is successful in exceeding the current standard of care for Ph+ B-ALL patients, then it could be implemented as a more effective treatment for Ph+ B-ALL with fewer serious side effects that could harm patients' survival rates**.** Future directions identified by these trials include experimenting to find effective combination therapies, using TKIs and possibly other immunotherapies to increase survival rates in Ph+ B-ALL, and exploring the effectiveness of using immunotherapy to reduce the risk of relapse in T-ALL.

Conclusion

ALL is a malignancy of the B or T lymphoblasts that most commonly occurs in childhood (Chan 2023). B-ALL in particular has responded well to immunotherapy, especially when combined with chemotherapy. The three immunotherapies that are currently being used to treat B-ALL include BsAbs, ADCs, and CAR-T cells. These treatments have been impactful through reducing the need for chemotherapy and thus, the toxicities associated with it (Aureli 2023). However, unlike B-ALL, the use of immunotherapy in T-ALL has proven to be much less effective. Much of this is because researchers have struggled to find an antigen target that exclusively occurs on malignant T lymphoblasts (Caracciolo 2023)**.** Current work is focused on finding an effective way to treat T-ALL with immunotherapy, especially when it comes to reducing the risk of relapse. For B-ALL, scientists are focused on finding the most effective combination of immunotherapies and chemotherapy, as well as reducing the current severe side effects of CAR-T cell therapy (Aureli 2023). The use of CAR-NK cells (Aureli 2023) or Sig15 (Abukharma 2023) to treat B-ALL and TKIs to treat Ph+ B-ALL (NCT04530565) are also under investigation. While immunotherapy may never completely replace chemotherapy in the treatment of ALL**,** it certainly shows promise to significantly reduce the need for chemotherapy and its associated toxicities. While all patients will no doubt benefit from the reduction of these severe side effects, those who are 60+ especially stand to gain. Though their prognosis remains grim now, it is safe to say that they can look forward to a much more positive prognosis and life expectancy in the near future.

References

1. Aureli, A., Marziani, B., Venditti, A., Sconocchia, T., & Sconocchia, G. (2023). Acute lymphoblastic leukemia immunotherapy treatment: Now, next, and beyond. *Cancers*, *15*(13), 3346
2. Caracciolo, D., Mancuso, A., Polerà, N. *et al*. The emerging scenario of immunotherapy for T-cell Acute Lymphoblastic Leukemia: advances, challenges, and future perspectives. *Exp Hematol Oncol* **12**, 5 (2023). https://doi.org/10.1186/s40164-022-00368-w
3. Kantarjian, Hagop MD; Jabbour, Elias MD. Acute Lymphoblastic Leukemia: Research & Therapy in 2021. Oncology Times 43(17):p 1,11,12,18, September 5, 2021. | DOI: 10.1097/01.COT.0000791796.99084.b2
4. Matthew J. Wieduwilt; Ph+ ALL in 2022: is there an optimal approach?. *Hematology Am Soc Hematol Educ Program* 2022; 2022 (1): 206-212. Doi: https://doi.org/10.1182/hematology.2022000338
5. NCT04530565
6. NCT05277753
7. Pillsbury, C. E., Dougan, J., Rabe, J. L., Fonseca, J. A., Zhou, C., Evans, A. N., Abukharma, H., Ichoku, O., Gonzalez-Flamenco, G., Park, S. I., Aljudi, A., DeRyckere, D., Castellino, S. M., Rafiq, S., Langermann, S., Liu, L. N., Henry, C. J., & Porter, C. C. (2023). Siglec-15 Promotes Evasion of Adaptive Immunity in B-cell Acute Lymphoblastic Leukemia. *Cancer research communications*, *3*(7), 1248–1259. https://doi.org/10.1158/2767-9764.CRC-23-0056
8. Puckett Y, Chan O. Acute Lymphocytic Leukemia. [Updated 2023 August 26]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459149/