The Effectiveness of CAR T-cell Therapy as Treatment for Acute Lymphoblastic Leukemia

Abstract

B-cell acute lymphoblastic leukemia (B-ALL) is the presence of an over proliferation of immature B lymphocytes. These immature cells are unable to participate in immune responses and leave the patient susceptible to persistent infections. When diagnosed early, B-ALL has a relatively high survival rate. However, when this type of leukemia shows chemotherapy resistance, the survival rate drops significantly. Anti-CD19 CAR T-cell therapy presents an alternative treatment option. With a response rate greater than the FDA approved clofarabine and a low risk for GVHD, CAR T-cell therapy is a promising treatment for most patients with refractory B-ALL. Anti-CD19 CAR T-cell therapy increases the likelihood of achieving a negative minimum residual disease (MRD) for refractory patients, and therefore, allows them to progress to long term treatments such as hematopoietic stem cell transplantation (HSCT).

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An estimated 150,000 new cases of leukemia, lymphoma, and myeloma were reported in 2013. This incidence accounts for about 9% of new cancer cases in the United States (McKenzie et al., 2015). Nearly half of all diagnosed leukemias are acute leukemias. These acute leukemias are most prevalent among children age 2 to 5 and adults older than 50. B-cell acute lymphoblastic leukemia (B-ALL) is the most common form of leukemia in children (Lee et al., 2015). B-ALL has a 90% survival rate in children, but the prognosis drops significantly to about 10% in those patients who do not respond to chemotherapy. Acute Lymphoblastic Leukemia (ALL) is typically diagnosed upon the presence of at least 20% immature lymphocytes known as lymphoblasts. The use of chimeric antigen receptor T-cells (CAR T-cells) seems to be a promising treatment for those diagnosed with lymphoblastic leukemias, particularly for those not responding to chemotherapy.

Chimeric antigen receptors (CAR) are artificially created T-cell receptors designed to target specific antigens on tumor cells as well as activate internal cell signaling of cytotoxic T lymphocytes. CD19 is the most favorable target antigen for B-cell malignancies because it is only expressed on B-cells and no other normal cell lines or pluripotent hematopoietic stem cells (Zhang et al., 2015). The anti-CD19 CAR T-cell production process begins with lymphocyte apheresis to collect a sufficient number of CD3+ lymphocytes. Apheresis is the mechanical process of removing a person's blood, separating it into components, and returning only the components that are not needed back to the donor. The cell collection process can be autologous, using the patient's own cells, or allogenic, using a donor's cells. After the lymphocytes have been collected the T cells are modified using viral transduction to stimulate

the cells to produce the anti-CD19 CAR (Tumaini et al., 2013). The successfully modified cells are then cultured and stimulated to proliferate until a sufficient amount is available. The complete manufacturing process takes about eleven days to complete (Lee et al., 2015). Finally, the modified cells are delivered to the patient via venipuncture.

Research focusing on CAR T-cell therapy has gained attention, as earlier treatment methods based on "adoptive T cell immunotherapy" have shown to be less effective. CAR T-cell therapy has shown even greater response rate than the FDA approved treatment, clofarabine, and autologous lymphapheresis has proven to be a feasible option for most leukemic patients. Previous treatments such as donor lymphocyte infusion (DLI) have been associated with severe graft versus host disease (GVHD) (Ataca & Arslan, 2015). Graft versus host disease is a life-threatening disease in which donor cells recognize the host as foreign and attack host cells. It is important to continue research in this area to find treatments that are curative in most cases without causing potentially life threatening side effects.

Literature Review

Lymphapheresis. Many factors contribute to the effectiveness of CAR T-cell therapy as treatment for ALL. Since apheresis is the first step in the treatment process, it is important that an adequate number of T-cells can be obtained from patients with such malignancies. A common clinical finding in several leukemias is leukopenia, a decrease in circulating white blood cells. In recent meta-analysis, Allen et al. (2017) observed autologous lymphapheresis for the production of CAR T-cells to investigate the safety of the procedure and the attainability of lymphocytes for leukemic patients. Among the parameters analyzed were the CD3+ cell yields versus diagnosis and pre-apheresis cell count, as well as varying cell types versus CD3+ cell yield. Allen et al. (2017) concluded that for most patients, the lymphapheresis process is safe and effective,

although longer collection time is suggested to increase the number of CD3+ cells collected in patients at risk for low yields. However, studies supporting these findings are limited. All apheresis procedures in this study were performed using the COBE Spectra. This instrument is no longer supported and any future studies will be performed using Spectra Optia or Amicus (Allen et al., 2017). Instrument comparison will therefore be necessary in the future.

Dose and Response rate of CAR T-cells. While lymphapheresis may be the first step in the therapy process, it is even more important that CAR T-cells produce positive, observable responses in patients, and to determine the appropriate dose for administering CAR T-cells. Lee et al. (2015) conducted a dose escalation clinical trial of adults and children with ALL, to determine the maximum tolerated dose and response rate of anti-CD19 CAR T-cell treatment. The authors concluded that anti-CD19 CAR T-cell therapy is indeed a feasible option for most patients. Moreover, treatment produced a complete response in 70% of the patients with refractory B-cell ALL, 60% of patients were MRD-negative (minimal residual disease) and 78.8% of those patients remained MRD-negative four to eight months post treatment (Lee et al., 2015). The maximum tolerated dose in this study was defined as 1 X 10^6 CAR+ T-cells per kg; however, maximum tolerated dose is variable for each patient depending on the leukemic burden. Results reveal even greater response to treatment than the FDA approved treatment, clofarabine, which only has an 8% - 20% complete response (Lee et al., 2015). Nevertheless, the scope of these findings is limited in that most patients that achieved negative MRD eventually received hematopoietic stem cell transfusion, and the true longevity of response to anti-CD19 CAR T-cells could not be assessed. In addition, the study by Lee et al. (2015) was performed on patients who received previous leukemic interventions. Despite the limitations, anti-CD19 CAR

T-cell therapy has provided an acceptable response rate to patients with chemotherapy refractory leukemia.

Safety of CAR T-cell therapy. Finally, the toxicities and disadvantages of CAR T-cell therapy should be determined for optimal standard of care practices. In the trial performed by Lee et al. (2015), the most common toxicity observed was cytokine release syndrome (CRS). Patient with CRS present with varying symptoms including hypoxia, fever, and mild flu-like symptoms (Ataca & Arslan, 2015). In the study conducted by Lee et al. (2015), it was determined that this syndrome is completely reversible. Neurotoxicity and cytopenia were also among the toxicities noted by Lee et al. (2015), but were all corrected during treatment. The rate of toxicities noted is likely caused by the dose escalation this trial was based on. Improved knowledge is needed to reduce the rate of CRS and improve patient safety. No evidence of GVHD was observed (Lee et al., 2015).

Discussion

While B-ALL is the most common childhood cancer, the survival rate is about 90% with early diagnosis. Adults have a decreased survival rate with subtypes less likely to be chemotherapy sensitive. Prolonged therapy allowing the introduction of several toxicities and occurrence of refractory B-ALL, greatly reduce the survival to less than 10 % regardless of age (Lee et al., 2015). Anti-CD19 CAR T-cell therapy would be a great option for patients with refractory lymphoid leukemias not responding to chemotherapy. In Allen et al.'s (2017) meta-analysis, they concluded that leukemia patients with the common clinical presentation of leukocytopenia can still be autologous donors to their CAR T-cell production process. This study can be applied to a larger population which means this treatment option would be available to a broader range of patients. The study however, is limited due to the retrospective analysis.

Furthermore, the collection procedure was performed on outdated equipment, which limits future comparison in the area of lymphapheresis.

In the clinical trial directed by Lee et al. (2015), they found anti-CD19 CAR T-cell therapy has relatively high response rates, with the majority of patients observed achieving negative MRD and remaining MRD-negative for months after treatment. Lee et al. (2015) also noted some toxicities associated with the treatment. All toxicities were reversible, including the most common toxicity, CRS. The major limitation of this study was that patients achieving negative MRD eventually received HSCT, and the continued monitoring of treatment durability could not completed.

Conclusion

B-ALL is the most common form of leukemia in children. Although it has a relatively high survival rate, the chances of survival are significantly decreased if the cancer is not responsive to chemotherapy. CAR T-cell therapy, particularly anti-CD19 T-cells, show great potential for providing remission of B-cell ALL. The overall process effectively produces a complete response in leukemic patients, including those who have undergone unsuccessful chemotherapy treatments. CAR T-cells expressing anti-CD19 appear to have the greatest potential in increasing the survival rate among refractory B-ALL. CD19 is specific for B-cells so therapy targeted for this cell marker yield fewer adverse reactions. CRS is the major toxicity associated with treatment, but it is a reversible complication. Further knowledge of CRS is required to predict its occurrence and improve the safety of patients undergoing treatment with CAR modified T-cells. In addition to fewer toxicities, CAR T-cell therapy increases the likelihood of achieving MRD for refractory patients and allows them to progress to long term treatment procedures such as HSCT.

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