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# CAR T-cell Therapy for Acute Lymphoblastic Leukemia

Esther Langner

Esther Langner will graduate in June 2019 with a Bachelor of Science degree in Biology and will be attending Mercy College's Physician Assistant program.

## Abstract

*Despite all the available therapies, Acute Lymphoblastic Leukemia (ALL) remains extremely difficult to eradicate. Current available therapies, which include chemotherapy, radiation, and stem cell transplants, tend to be more successful in treating children than adults. While adults are more likely than children to relapse after treatment, the most common cause of treatment failure in children is also relapse. Improved outcomes for all ALL patients may depend upon new immunotherapies, specifically CAR T-cell therapy. CAR T-cell therapy extracts a patient's own T-cells and modifies them with a CD19 antigen. This modification allows the new T-cells to recognize and kill cancer cells that contain the antigen on their surfaces, like leukemia cells do. Although CAR T-cell therapy may cause toxicities such as Cytokine Release Syndrome (CRS), they are mostly short term and reversible. Trials indicate that almost all patients who undergo CAR T-cell therapy will enter complete remission. Though a large percentage of those patients will experience a relapse, relapse rates of CAR T-cell therapy are lower than other treatments. By reviewing the available research literature regarding CAR T-cell therapy, this paper examines the effectiveness of this therapy in different patient populations and demonstrates that CAR T-cell therapy significantly improves event-free survival rates in ALL patients.*

## Acronyms Used:

ALL - Acute Lymphoblastic Leukemia

ACT - Adoptive Cell Transfer

CAR - Chimeric Antigen Receptors

CRS - Cytokine Release Syndrome

CSF - Cerebrospinal Fluid

Ph - Philadelphia chromosome

TKI - Tyrosine Kinase Inhibitors

CNS - Central Nervous System

WBC - White Blood Count

## Introduction

The leading cause of disease related death in U.S. pediatric patients is cancer, most commonly Acute Lymphoblastic Leukemia (ALL) (Tumaini, et. al., 2013). For many years, cancer treatments were limited to radiation therapy, chemotherapy, or surgery. More recently, newer types of treatments called immunotherapies, have become available. Cancer immunotherapies are therapies that enlist and strengthen the power of a patient's immune system to fight and attack the cancer. Of the immunotherapies discovered, adoptive cell transfer (ACT), in which a patient's own immune cells are collected and used to treat their cancer, has achieved the most successful outcomes. The most effective ACT therapy is CAR T-cell therapy (Brentjens, et. al., 2013). In 2017, CAR T-cell therapy was approved by the FDA as a treatment for ALL and for adults with advanced forms of lymphoma. However, while it may seem that CAR T-cell therapy is poised to revolutionize cancer therapy, some of the optimism surrounding it is tempered by concerns about its safety and potentially severe toxicities (Lim, June, 2017), calling into question if CAR T-cell therapy is an improved treatment for ALL and relapsed ALL.

## Methods

The research used in this paper was located and compiled from papers obtained through Touro College's access to on-line publications. Google Scholar and Blood Journal were used for additional references. The articles were critically selected,

compared, and analyzed to evaluate if CAR T-cell therapy is an effective treatment for ALL.

## CAR T-cell Therapy

CAR T-cell therapy is relatively straight forward. T-cells, which play a critical role in orchestrating an immune response, are responsible for killing cells that are infected by pathogens. In order to retrieve these T-cells, blood is drawn from a patient and the T-cells are separated from the rest of the blood. The T-cells then undergo genetic modification via the insertion of genes that encode for tumor specific chimeric antigen receptors (CARs). These receptors allow the T-cells to recognize and subsequently attach to a specific antigen. The antigen CD19 was chosen because it is universally expressed on all ALL tumor cells and not on pluripotent hematopoietic stem cells (Tumaini, et. al., 2013). Once the T-cells have been successfully engineered to express the CD19 antigen, they are expanded in a lab to form hundreds of millions of cells. This process has been refined and advanced over the years and can now quickly create large quantities of T-cells that have genetically engineered receptors on their surface to treat both pediatric and adult ALL patients. The CAR T-cells are then infused back into the patient's body where they continue to multiply, recognize, and kill the cancer cells containing the antigen on their surfaces (Tumaini, et. al., 2013). This step is considered to be an in vivo expansion, which requires the new host to support these engineered T-cells. Therefore, the administration of the T-cells is preceded by a lymphodepleting regimen, as lymphopenia (the condition of having an abnormally low level of lymphocytes in the blood) generates changes that support T-cell expansion and survival (Klebanoff, et. al., 2005). As a result, most adoptive cell therapy protocols incorporate some version of lymphotoxic therapies prior to cell transfer.

Like most cancer treatments, CAR T-cell therapy has serious side effects. The most common side effect that patients usually experience is cytokine release syndrome (CRS). Notably, CRS has been seen in patients treated with other immunotherapies and is therefore not limited to CAR T-cell therapy (Lee, et. al., 2014; Teachey et al., 2013). CRS is caused by the cytokines

released from the T-cells as CAR T-cells rapidly expand within the patient's body. It can also be caused by other immune cells, such as macrophages that might produce cytokines in response to the cytokines produced by the infused CAR T cells. CRS patients have high levels of IL-6 (the cytokine secreted by the T-cells) and is characterized by systemic symptoms that usually begin with a fever (Giavridis, et. al., 2018). The onset of the fever can range from a few hours after the treatment to more than a week after CAR T-cell infusion (Brudno, Kochenderfer, 2016). The fever is followed by nausea, chills, headaches, muscle pain, and difficulty breathing (Maude et al., 2014).

CRS can lead to many different related toxicities that attack organ systems. Cardiovascular toxicities most commonly cause tachycardia, although more severe cases of CRS have prompted hypotension, arrhythmia (irregular heartbeat), and decreased cardiac ejection fraction. CRS can lead to pulmonary edema and hypoxia, the deficiency in the amount of oxygen reaching the tissues that may require mechanical ventilation. It can also lead to reduced renal perfusion, the volume of blood delivered to the kidneys per unit time, which can cause a kidney injury. However, CAR T-cell related renal injuries are mostly reversible. The same goes for other laboratory abnormalities that CRS causes, such as elevated levels of bilirubin and/or serum transaminases. Patients also commonly become neutropenic and lymphopenic when undergoing and following CAR T-cell therapy because they are severely immunocompromised and are not protected against opportunistic infections, such as salmonella, bacteremia, and urinary tract infections. Viral infections such as influenza, respiratory syncytial virus, and herpes zoster virus, have also been known to affect patients following CAR T-cell infusion (Brudno, Kochenderfer, 2016). Unfortunately, in such a setting, fevers, tachycardia, hypotension, and other regular symptoms associated with CRS can be difficult to differentiate from sepsis, which is a life-threatening infection. In an early trial, a patient with chronic lymphocytic leukemia who received chemotherapy prior to his CAR T-cell treatment died with fever, hypotension, and renal failure four days after the administration of the CAR T-cells. It was discovered later that there were elevated serum levels of inflammatory cytokines before CAR T-cell infusion, suggesting that the patient had a prior infection that caused his death (Brentjens, Curran, 2012).

CAR T-cell therapy also has neurological toxicities associated with the treatment. The toxicities can be diverse, as they do not always localize to one specific area of the nervous system. The occurrence of neurologic toxicity is quite variable, with published reports stating that there is a 0% to 50% chance of neurological toxicities developing (Brudno, Kochenderfer, 2016). Neurologic events are not always associated with CRS toxicities, which suggests that in some cases, they might have a different mechanism than many of the other usual toxicities caused by CRS, such as fever and hypotension (Maude, et. al., 2014).

Ironically, CRS is considered to be an “on-target” effect of CAR T-cell therapy, as the presence of the cytokines show that the T-cells are working in the body. Various grading systems for the “CRS-related adverse events” caused by immunotherapies have been proposed. They depend on many things, such as the temperature of the fever, the number of severe signs of toxicities, and cytokine levels in the patient. A category of severe CRS is defined as CRS requiring pharmacologic and medical intervention. In such cases, tocilizumab, an IL-6 receptor antagonist that is used to treat rheumatologic disorders, is used as a first line agent. While not approved for this use by the FDA, it has effectively treated CRS-related toxicities in clinical trials with no life threatening or toxic effects (Maude, et. al., 2014), and is now a widely used off-label for the patients who have received CAR T-cell infusions. (Brudno, Kochenderfer, 2016).

Systemic corticosteroids have also been used for CRS-related toxicities. However, there is some evidence that corticosteroids can possibly inhibit CAR T-cell persistence and anti-malignancy efficacy. For this reason, corticosteroid therapy is only used as a last resort if the tocilizumab does not succeed in ameliorating the CRS. However, because neurologic toxicities may not come along with CRS, these toxicities may differ from that of CRS alone. It is unclear if tocilizumab has any beneficial effect on neurologic toxicities, as severe neurologic toxicities are commonly treated with systemic corticosteroids right away, rather than initially beginning with tocilizumab.

Toxicities caused by CAR T-cells are diverse. Management of these toxicities requires continuous and vigilant monitoring, aggressive supportive treatments, and, in some cases, intensive care. Another harmful side effect of CAR T-cell therapy is that the engineered CAR T-cells with the CD-19 receptor could damage other tissues that express the antigen recognized by it. This mechanism of toxicity can be mostly eliminated by searching for any expression of the targeted antigen on normal tissues in the body prior to the development of the CAR (Lamers, et. al., 2013).

### Other Therapies

There are several other therapies used to treat ALL. The goal of these treatments is to remove all traces of the ALL from the patient. The most commonly used treatment for ALL is chemotherapy. The chemo treatment is divided into three phases. The first stage is known as the induction phase and usually takes about a month. The next phase, consolidation, also referred to as intensification, is, as its name suggests, extremely intense as well, and typically lasts for a few months. The last phase, maintenance, or post-consolidation, is less intensive, and lasts for about two years (Pui, et. al., 2008).

The goal of induction, is to remove more than 99% of the initial leukemia cells from the patient and to restore normal haemopoiesis, the production of blood cells and platelets in the bone marrow. Afterwards, if both the blood and bone marrow

show no evidence of persistent leukemia and blood counts have returned to normal, then the patient achieves remission. Studies show that 96 to 99% of children with ALL enter remission after the induction treatment. Adults have a lower remission rate with only 78-93% of adults entering clinical remission (Pui, et. al., 2008). Nevertheless, a remission is not necessarily a cure, and since the first month is such intense treatment, many complications and serious infections can arise. As a result, this phase of treatment requires lengthy hospital stays and frequent visits to the doctor, as these complications can be life-threatening. Recent advances in supportive care have helped lower these complication rates, making them considerably less common than they have previously been. Examples of supportive care are better nursing care, proper nutrition, prescribed antibiotics, and red blood cell or platelet transfusions as needed (Locatelli, et. al., 2012).

There are three major types of drugs that children with standard-risk ALL receive during the first month of treatment. These are chemotherapy drugs L-asparaginase and vincristine, as well as a steroid drug, usually dexamethasone (Goekbuget, et al., 2005). For children in high-risk groups, a fourth drug from the anthracycline class, typically daunorubicin, is added. ALL patients also require chemotherapy via the cerebrospinal fluid (CSF), as there may be leukemia cells that spread to the brain and spinal cord. This treatment is known as intrathecal chemotherapy and given through a lumbar puncture/spinal tap. Patients with high risk leukemia or leukemia in their CSF receive this treatment more frequently than other ALL patients do. In the past, along with intrathecal therapy, patients were also given prophylactic cranial irradiation. Recent studies have found that children who are given more intensive chemotherapy may not need radiation therapy at all. Doctors try to avoid giving radiation to the brain, especially in younger children, because even low doses may result in problems with cognition, growth, and development (Locatelli, et al., 2012).

The next phase, consolidation, is the phase of chemotherapy that further reduces the number of leukemia cells still in the body. Several chemo drugs are used together to prevent the remaining leukemia cells from developing a resistance. Intrathecal therapy is continued at this time, and patients with high-risk leukemia usually receive more intense chemotherapy. During this phase, patients with Philadelphia chromosome-positive ALL may benefit from the addition of other types of cancer therapies, such as targeted cancer drugs or stem cell transplants (Pui, et. al., 2008).

If the leukemia remains in remission after induction and consolidation, the third phase, maintenance therapy, can begin. Most treatments use medication given either as pills or intravenously, and a steroid, usually prednisone or dexamethasone. Depending on the type of ALL and the risk of recurrence, other drugs may be added as needed. In the beginning of the maintenance phase, most treatment plans include one or two repeat intensified treatments like the initial induction. These four-week

intensifications are called re-induction or delayed intensification. Some children at higher risk may receive more intense maintenance chemotherapy and intrathecal therapy. The total length for the three phases of chemotherapy for most ALL treatment plans is two to three years. However, patients with a higher risk of relapse are given several extra months of treatment as an added precaution (Pui, et. al., 2008).

Throughout the entire chemotherapy process, the combination of anti-cancer drugs used often causes serious side effects. This is mainly because the chemotherapy drugs affect healthy body cells as well cancer cells. Many organs, such as the kidneys, liver, testicles, ovaries, and lungs, can be damaged by these drugs. In an effort to reduce the number of side effects, the chemotherapy is given in cycles, and each round of treatment is followed by a rest period, so the body has time to recover. Some of the main side effects of chemotherapy are loss of hair and appetite, vomiting and nausea, constipation, and mouth sores. Chemo drugs also affect the normal cells in bone marrow, which can lower blood cell counts. This leads to an increased risk of infections, due to low white blood cell counts, easy bleeding and bruising from low platelet counts, and constant fatigue and shortness of breath, as patients do not have enough red blood cells (hemoglobin) to carry the oxygen needed in their bodies (Pui, et. al., 2008).

As with most treatments, steps can be taken to reduce the toll these side effects can have on the patients. Drugs, such as Ondansetron (Zofran) can be given to decrease nausea and vomiting. Transfusions or drugs can be administered to raise a platelet or red blood cell count, and antibiotics are given at the earliest sign of a developing infection. Even tumor lysis syndrome can be prevented. This potentially life-threatening side effect of chemo is usually seen in the induction phase of treatment. As the leukemia cells are killed by the chemo drugs, they break open, releasing their contents into the bloodstream. These components can overwhelm the kidneys because they are unable to filter out and remove all these substances from the blood at once, and the excess amounts of certain minerals can affect the heart and nervous system. Administering certain drugs and extra fluids during treatment can help the body eliminate these substances (Goldman, et. al., 2001). Patients need to be carefully monitored while being treated with cancer drugs to reduce the risk of these side effects as much as possible.

High-energy radiation used to kill cancer cells is another therapy used to treat ALL. Most often, external beam radiation therapy is used, in which a machine delivers a beam of radiation to a specific part of the body at a certain angle. Although radiation is not used as the main treatment for ALL, it is used in certain situations, such as preventing or treating leukemia that has spread to the brain, (though lately, radiation has been omitted from treatment plans) spinal fluid, and testicles. Before a bone marrow or peripheral blood stem cell transplant takes place,

the whole body often needs radiation. Rarely, radiation can help shrink a tumor if it is causing breathing problems by pressing on the trachea, although chemotherapy is often used instead, as it normally achieves the same effect more rapidly (Cherlow, et. al., 1993). The side effects of radiation therapy depend on the location at which the radiation beam was targeted. The treated area can appear sunburned and undergo hair loss. Radiation to the abdomen can sometimes cause nausea, vomiting, or diarrhea. Effects of radiation that targets large parts of the body may include fatigue, shortness of breath, and an increased risk of infection due to lower blood cell counts (Pearce, et. al., 2012).

One of the most serious, but not very common side effects of ALL chemotherapy and radiation therapy is an increased risk of getting another neoplasm, a new and abnormal growth of tissue in some part of the body that can become cancerous later on. Although effective treatments for ALL now result in five-year survival rates above 70%, the treatments used are ironically carcinogenic. Studies show that there is a substantial chance of secondary neoplasms among patients treated for ALL with chemotherapy and radiation. Children five years old and under, as well as patients who received radiation as a form of therapy, are at a higher risk for second tumors arising in their central nervous system, as well as patients who received radiation as a form of therapy. (Neglia, et. al., 1991).

Allogenic hematopoietic stem-cell transplantation, the transplantation of multipotent hematopoietic stem cells, is the most intensive form of treatment for ALL. This stem cell transplantation seems to benefit several types of high risk ALL patients, such as patients with poor initial responses to treatments, patients who have relapsed, and those with Philadelphia chromosome-positive disease (Pui, et. al., 2008). The Philadelphia chromosome (Ph) is the most frequent cytogenetic abnormality in adult ALL. Most patients with Ph+ ALL cannot be treated with chemotherapy alone, as chemotherapy can only induce a complete remission for a few months until most patients experience a relapse. The five-year survival rates for those who have Ph+ ALL and were treated with chemotherapy alone are less than 10%. However, those who underwent allogenic stem cell transplantation during early remission have a 35-65% chance of long-term survival (Lee, et. al., 2005). Bone marrow transplants (BMT) are sometimes needed as well for patients with underlying malignancies or genetic disorders (Slavin, wt. al., 1998).

Targeted cancer drugs are also being used as a treatment for ALL. Cancer cells are cells that undergo changes to their genes. These changes cause the cancer cells to grow faster and work differently from others. Targeted cancer drugs use these differences in cell genes to differentiate them from other normal cells and target the specific gene changes. The main targeted cancer drugs used for ALL are tyrosine kinase inhibitors (TKIs). They block tyrosine kinases, chemicals that cells use to signal to each other. The main side effects of targeted cancer drugs, specifically

TKIs, are fatigue, a sore mouth, rashes or reddening of the skin, and loss of appetite (Pui, et. al., 2008).

### Success Rates

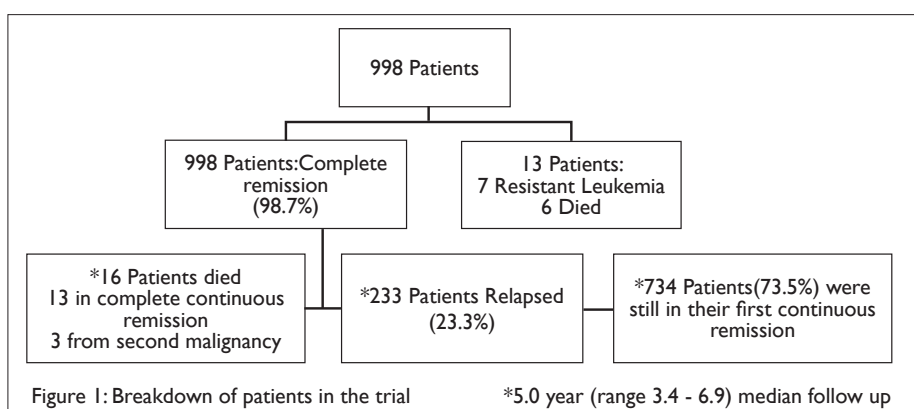
Chemotherapy affects children and adults with ALL differently. Children that undergo chemotherapy treatment have a much greater chance of survival than adults, yet only 80 – 85% of children can be cured. A large chemotherapy trial comprised of children up to eighteen years old was conducted on 1,114 patients. Of those patients, only 998 became protocol patients, and were divided into three groups; a standard risk group, those without central nervous system (CNS) disease, a risk group, those with CNS disease, and an experimental group. They all received induction therapy and some variation of continued chemotherapy, including cranial irradiation as needed. Additionally, an intensive reinduction therapy was added for patients in the standard risk group who had increased risk of failure during the trial. The event-free survival for the 110 patients who did not receive reinduction therapy was almost 30% lower than those with reinduction therapy. In this trial, a complete remission was measured by several parameters: the absence of leukemic cells in the blood and CSF, fewer than 5% lymphoblasts in marrow, and no evidence of localized disease. Relapse was defined as reappearance of lymphoblasts or localized leukemia infiltrates at any site (Reiter, et. al., 1994).

Figure 1 presents results of this trial. Of the 998 patients, 985 (98.7%) entered complete remission. Thirteen patients did not enter remission; seven had resistant leukemia, one died of renal failure, and five died an early toxic death. At the 5.0-year (range 3.4 - 6.9 years) median follow up, 233 patients experienced a relapse (23.3%). Thirteen more patients died while in complete, continuous remission and three patients developed a second malignancy. There were 734 patients (73.5%) still in their first continuous complete remission.

The six-year, event-free survival estimate was for 888 patients. The 110 patients who did not receive reinduction were excluded from this estimate. Of all three branches together, the estimate was  $74\% \pm 2\%$ . Detailed analysis showed that male patients had higher white blood counts (WBC), were six years old or greater, or had T-ALL, had a better outcome than others. For example,  $69\% \pm 5\%$  of T-ALL patients with  $WBC \geq 20,000/\mu L$  had event-free survival at six years. This is a comparatively larger number than  $58\% \pm 3\%$  for the complementary group of patients with an immunophenotype other than T-cell ALL. These other immunophenotypes had no predictive strength for treatment outcome (Reiter, et. al., 1994).

There was a trial for 525 patients under 19 with a first-time relapse of T-cell or B-cell ALL. The patients were treated with intensified, short course multi drug chemotherapy. A major aim of this study was to improve outcomes through a third intensive chemotherapy course (R3) containing HD cytarabine and





etoposide. Results showed that 440 patients (84%) achieved a second complete remission, 25 patients (5%) died during induction, and 60 patients (11%) did not respond to treatment. Thirty-one patients (6%) died in the second complete remission as a result of treatment-related adverse effects. Of those patients who achieved second complete remission, 246 patients (56%) suffered subsequent relapse, and six patients (1%) experienced a secondary malignant neoplasm. At a median follow-up of twelve years, 153 (29%) of 525 patients remained in complete continuous remission. The study concluded that neither R3 nor adaptation of chemotherapy intensity was capable of improving event-free survival or of overcoming prognostic factors. Therefore, induction regimens need to be improved for high risk patients, and allogeneic stem cell transplant should be recommended in patients achieving second complete remission (Tallen, et. al., 2010).

Adult recovery rates are not as high as children's. ALL accounts for about 15 – 20% of all adult leukemias. Although some of these patients enter complete remission, most of them relapse and die. With chemotherapy alone, those younger than sixty have a 30 - 40% chance of recovery (Mohty, et. al., 2010). Anyone older than sixty has less than 10% chance. In many cases, chemotherapy is not enough and adult patients need other therapies, such as transplants. However, the patients still need to undergo chemotherapy maintenance after the induction therapy and transplant. (Goldstone, et. al., 2008).

A study was performed on 609 adults with relapsed ALL, all of whom were previously treated in the Medical Research Council study, in which the overall survival of newly diagnosed patients was 38% at 5 years. By contrast, in this chemotherapy study, the overall survival at 5 years after relapse was 7%. Factors predicting a good outcome after salvage therapy were young age (overall survival of 12% in patients younger than 20 years vs overall survival of 3% in patients older than 50 years) and short duration of first remission. Treatment received in the first complete remission did not influence the outcome after relapse. This study concluded that adults who have an ALL relapse cannot be rescued using currently available therapies, even if stem

cell transplantation is available. Prevention of recurrence would be the best strategy for long-term survival from this disease (Fielding, et. al., 2007).

The most common cause of ALL treatment failure is relapse, as approximately 15 – 20% of children experience relapse. With intensive chemotherapy and transplantations, 30-50% of all children with relapsed ALL can be cured. However, because relapsed ALL is

difficult to treat, most relapsed children still die, despite the aggressive therapies (Locatelli, et. al., 2012). CAR T-cell therapy may be able to overcome the limitations of conventional therapies and induce remission in patients with relapsed and refractory ALL (Maude, et. al., 2014). In one trial, thirty patients were selected. Twenty-five patients were aged from five to twenty-two, and the other five patients between twenty-six and sixty. Of these patients, twenty-six had B-cell ALL in a first to fourth relapse, three had primary refractory B-cell ALL, and one patient had relapsed T-cell ALL. Eighteen patients had experienced their relapsed ALL after allogeneic stem-cell transplantation. All the patients in this study experienced CRS. Eight patients developed severe CRS, and all required respiratory support and vasopressor support for hypotension. However, all neurotoxicity was reversible and there was no lasting damage from the CRS (Maude, et. al., 2014).

One month after the infusion, twenty-seven patients (90%) obtained complete remission. Of these patients, nineteen remained in remission. Fifteen patients received no further therapy, and five withdrew to receive other treatments. At six months, the event-free survival rate was 67%, and the overall survival rate was 78%. This is a much better rate than the <25% complete remission rates of the recently approved drugs (nelarabine, liposomal-encapsulated vincristine, and clofarabine) for ALL. This study showed an encouraging sustained remission of up to two years (Maude, et. al., 2014).

In another trial, 53 pretreated adults received CAR T-cell therapy. A total of thirty-six patients (68%) received CAR T-cell therapy as a third or later salvage treatment, twelve had primary refractory disease, nineteen had undergone allogeneic hematopoietic stem-cell transplantation previously, and thirteen had received the drug blinatumomab previously. A total of sixteen patients had Philadelphia chromosome positive ALL, and ten of the sixteen patients had disease that was refractory to the drug ponatinib. After infusion, 26% of the patients had severe CRS. Complete remission was defined as less than 5% bone marrow blasts, the absence of circulating blasts, and no extramedullary sites of disease regardless of cell-count recovery. Relapsed

disease was defined as the reappearance of blasts in blood or bone marrow or in an extramedullary site after a complete remission. One patient died from multiorgan failure and severe CRS on day five, and complete remission was observed in 83% of the patients. At a median follow-up of twenty-nine months (range one to sixty-five), the median event-free survival was 6.1 months, and the overall survival was 12.9 months. Patients with a low disease burden (<5% bone marrow blasts) before treatment had distinctly enhanced remission duration and survival, with a median event-free survival of 10.6 months and a median overall survival of 20.1 months. Patients with a higher burden of disease ( $\geq 5\%$  bone marrow blasts or extramedullary disease) had a greater incidence of the cytokine release syndrome and neurotoxic events and shorter long-term survival than did patients with a low disease burden. This is a better outcome than the three to nine months of median overall survival seen from chemotherapy (Park, et. al., 2018).

Of the 44 patients who had a complete remission after the infusion of CAR T-cells, 26 did not undergo further therapy, including nine who were alive and seventeen who had a relapse or died. One patient received alternative treatment for minimal residual disease–positive disease, and seventeen patients progressed to transplantation. The median time from the CAR T-cell infusion to transplantation was 74 days (range, 44 to 312). Of the seventeen patients who underwent allogeneic transplantation after the CAR T-cell infusion, five patients were alive and had a complete remission, six had a relapse, and six died from transplant-related toxic effects. This study showed that CAR T-cell therapy had favorable long-term remission rates in a population of patients with low disease burden, who had significantly longer event-free survival and overall survival with markedly lower incidences of toxic effects than did those with a high disease burden (Park, et. al., 2018).

In another trial, 20 patients (aged 1-30 years, including eight patients who underwent allogeneic stem-cell transplantation) with relapsed or refractory ALL were infused with CAR T-cells. CRS was recorded in 16 patients, and all toxicities associated with the therapy were reversible. Complete remission was observed in 70% of the patients. Many of the patients in the trial underwent further stem cell transplantation therapy, which led to the conclusion that CAR T-cell therapy is an effective bridge to stem cell transplantation for patients with chemo refractory B-ALL. Because most patients who entered remission eventually underwent stem cell transplantation, this study was not able to assess the durability of response to the CAR T-cells, yet it was associated with a favorable long-term survival. Additionally, this study showed that CAR T-cells mediate a complete remission in refractory ALL that is substantially higher than the 8-20% reported with clofarabine, a drug that was approved in 2004 for refractory pediatric ALL (Lee, et. al., 2014).

## Conclusion

CAR T-cell therapy is currently being used as a treatment for patients who have already been treated with other therapies and relapsed. This makes the effectiveness of the therapy difficult to gauge, as CAR T-cell therapy trial outcomes cannot be compared to first time treatment data of other therapies such as chemotherapy. Nevertheless, the trials have shown that the toxicities from CAR T-cell therapy are manageable and are no longer a big concern. The trials also show that although it does not have perfect results, CAR T-cell therapy is far more successful in treating relapsed ALL than other therapies have been, as the complete remission rates and longer survival rates are higher for relapsed ALL than any other treatment. Some studies indicated that many patients may have needed additional stem cell transplants and other therapies after undergoing CAR T-cell therapy, so it cannot always be used as a lone therapy. However, some patients did achieve event-free remission from only CAR T-cell therapy. There were no attempts in proving that CAR T-cell therapy should not be done, making this therapy a great treatment option for ALL, especially relapsed ALL.

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