Review Article

Cart Cell: A Living Drug to Treat Cancer

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ABSTRACT

Cancer is a group of diseases characterized by uncontrolled proliferation of normal cells with potential capacity to invade or spread to other parts of the body. The underlying cause of the disease may be environmental factor or inherited genetics, in which tobacco is the leading cause. Currently available treatment option for cancer is surgery, radiation and chemotherapy. Advancement in the field of biotechnology leads to the development of targeted therapies like immunotherapy which can be used in combination with conventional therapy. Chimeric Antigen Receptor T (CART) cell therapy is a newly emerged therapy for cancer in which studies shows a great response, even though conventional therapy fails. In 2017 US FDA approved two CART cell therapies, Tisagenlecleucel and Axicabtagene Ciloleucel for Acute Lymphoblastic Leukemia (ALL) and Diffuse Large B Cell Lymphoma (DLBCL) respectively which is refractory to conventional therapy. Ongoing researches in CART cell therapy gives a hope for miracle cure in cancer.

Keywords: Acute Lymphoblastic Leukemia (ALL), Cancer, CART Cell and Immunotherapy.

INTRODUCTION

Cancer is a generic term for a large group of diseases characterized by the growth of abnormal cells beyond their usual boundaries that can then invade adjoining parts of the body and/or spread to other organs. It is characterized by progressive, persistent, perverted, purposeless and uncontrolled proliferation of tissues[1]. Depending upon the type of cell, the tumor cells resemble, cancer can be classified into sarcoma, carcinoma, blastoma, lymphoma, leukemia etc. It can affect any part of the body and has many anatomic and molecular subtypes that each requires specific management strategies.

Environmental factors and inherited genetics are the underlying causes of cancer. Environmental factors (tobacco, diet and obesity, radiation, infection, lack of physical activity) contribute 90-95% risk for cancer while genetic mutation accounts for only 5-10%[2-3].

According to WHO, Cancer is the second leading cause of death worldwide and accounts for 8.8 million deaths in 2015. For many years, cancer has been managed by surgery, radiation and chemotherapy. After the emergence of Targeted therapies like monoclonal antibodies (e.g., Imatinib, Trastuzumab), it became the standard treatment for many cancers over the last two decades. But over the past several years, immunotherapy like Chimeric Antigen Receptor T cell therapy emerged as what many in the cancer community now call the "fifth pillar" of cancer treatment[4]. The emergence of Chimeric Antigen Receptor T cell therapy gives a new hope in cancer treatment.

Initially, the use of CART cell therapy has been restricted to small clinical trials, largely in patients with advanced blood cancers. But these treatments have nevertheless captured the attention of researchers and the public alike because of the remarkable responses they have produced in some patients both children and adults for whom all other treatments had stopped working.

In 2017, two CART cell therapies were approved by FDA. Tisagenlecleucel for the management of children with Acute Lymphoblastic Leukemia (ALL) and Axicabtagene Ciloleucel for adults with advanced Lymphomas.

CART CELL THERAPY

Immunotherapy can be explained as therapies that enlist and strengthen the power of a patient's immune system to attack tumors. Among the immunotherapy like monoclonal antibodies, oncolytic virus therapy, Adaptive Cell Transfer (ACT), and cancer vaccines, ACT is the rapidly emerging immunotherapy in which patient's own immune cells are used to treat cancer. CART cells are one among the

several ACT that has advanced the furthest in clinical development.

In CART cell therapy, T cells are genetically engineered to express an artificial T cell receptor (i.e. Chimeric Antigen Receptor) through which they are targeted to disease related antigens[5]. When these CART cells come in contact with antigens on the tumors, they get activated and become cytotoxic. The CART cell destroy the cancer cell through mechanisms such as extensive stimulated cell proliferation, cytotoxicity, and by release of cytokines from immune cells that have an effect on other cells in the organism[6].

CD19, a transmembrane glycoprotein in human is widely expressed during all phases of B cell development until terminal differentiation into plasma cells. So CD19 can be effectively used as a B cell marker to diagnose cancers that arise from this type of cell-notably B cell lymphomas, Acute Lymphoblastic Leukemia, and Chronic Lymphocytic Leukemia (CLL)[7-9]. Thus CD19 targeted therapies based on T cells that express CD19 specific Chimeric Antigen Receptors (CAR) can be used for its antitumor activity in patients with $CD19^+$ lymphoma and leukemia. CAR-19 T cells are more effective than anti CD19 immunotoxins as it can remain in the body for a long period.

MILESTONES TO CART CELL THERAPY

In 2009 Noello Frey from Abramson Cancer Center of the University of Pennsylvania conducted a phase 1 study on “CART 19 to treat B cell leukemia or lymphoma that are resistant or refractory to chemotherapy”. Twenty-six participants were included in the study. Among this eighteen were diagnosed with Chronic Lymphocytic Leukemia (CLL) and eight with Acute Lymphoblastic Leukemia (ALL). Fourteen participants from eighteen completed the study and three of them had complete response (21.4% CR), three had partial response (21.4% PR) and eight had no response (57.1% NR). In ALL group with eight participants, six completed the study with 83.4% complete response and 16.6% no response[10].

Stephen A Grupp from Children’s Hospital of Philadelphia, Pennsylvania conducting a study on “Phase I/IIA study of CART 19 cells for patients with chemotherapy resistant or refractory $CD19^+$ leukemia and lymphoma (Pedi CART19)” since 2011. Seventy-six participants (children and adult of age 1 to 24) were included in the study. This study is still going on[11].

These two studies led collaboration of Children’s Hospital of Philadelphia with University of Pennsylvania and Novartis and done a pilot trial at Children’s Hospital of Philadelphia in 2014 October. This trial was titled as “CTL019 lentiviral vector in patients with relapsed/ refractory ALL at dose of 0.76×10^6 to 20.6×10^6 per Kg body weight”.

Out of the thirty participants (children and adult) in this study, twenty-seven had complete response (90%); fifteen among the twenty-seven were even refractory to stem cell transplantation[12]. This study was the base for US FDA approval for CART cell therapy for treating ALL in 2017.

In April 2017, Tisagenlecleucel (formely CTL019) received breakthrough therapy designation by US FDA for the treatment of relapsed or refractory diffuse large B cell lymphoma (DLBCL) and in August 2017 FDA granted approval for the use of Tisagenlecleucel in people with ALL. Approximate cost of therapy is 475000 USD.

In the same year FDA approved Axicabtagene Ciloleucel as breakthrough designation for B cell lymphoma. 373000 USD is the approximate cost for Axicabtagene Ciloleucel therapy.

PROCEDURE

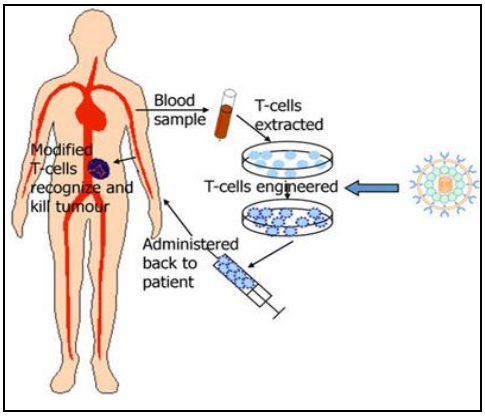

Fig. 1: showing CART Cell therapy procedure

In CART cell therapy WBCs are collected from the patient’s blood for preparing genetically modified T cells by Leukapheresis. It is a specific type of apheresis in which one particular constituent of blood is separated and return the remainder to the circulation[13]. During leukapheresis, sometimes calcium level can drop and cause numbness and tingling or muscle spasms. This can be easily treated with calcium, which may be given orally or intravenously.

Once the WBCs are removed, T cells are separated and genetically altered by adding the specific Chimeric Antigen Receptor. Thus T cell gets transformed to CART cell. This

process may take few weeks because a very large number of CART cells are needed for this therapy. When enough CART cells are produced they will be transplanted back to the patient to launch a precise attack against the cancer cells.

When these CART cells enter into the body they will specifically recognize the $CD19^+$ B cell. Once the CART cells start binding with cancer cells, they multiply and can destroy more cancer cells. This means when T cells are engineered to become CART cell, it acts as a "living drug"[14]. So CART cells are equivalent to a live drug for cancer therapy.

A few days before a CART cell infusion, a patient receive chemotherapy known as immunodepleting chemotherapy to lower the number of other immune cells so that the CART cells have a better chance to get activated and fight with the cancer cell.

TISAGENLECLEUCEL

Indication for the treatment of patients up to 25 years of age with B cell precursor acute lymphoblastic leukemia (ALL) that is refractory or in second or later relapse.

Dose: is given according to the body weight of the patient. For patients with 50Kg or less body weight 0.2 to 5.0 $\times$ 10^6 CAR-positive viable T cells per Kg body weight is given. For patients above 50Kg body weight dose is 0.1 to 2.5 $\times$ 10^8 CAR-positive viable T cells per Kg body weight.

Administration

one treatment course consists of lymphodepleting chemotherapy (30mg/m^2 intravenous Fludarabine daily for four days and 500mg/m^2 intravenous Cyclophosphamide daily for two days starting with the first dose of Fludarabine) followed by infusion of Tisagenlecleucel. Infusion of Tisagenlecleucel is given after two to fourteen days after completion of lymphodepleting chemotherapy.

AXICABTAGENE CILOLEUCEL

Indication for the treatment of adult patients with relapsed or refractory large B cell lymphoma after two or more lines of systemic therapy.

Dose: 2 $\times$ 10^6 CAR- positive viable T cells per Kg body weight, with a maximum of 2 $\times$ 10^8 CAR-positve viable T cells.

Administration

lymphodepleting chemotherapy regimen of Cyclophosphamide 500mg/m^2 intravenously and Fludarabine 30mg/m^2 intravenously on the fifth, fourth and third day before infusion of Axicabtagene Ciloleucel. After that administering Acetaminophen 650mg PO and Diphenhydramine 12.5mg intravenously or PO approximately one hour before Axicabtagene Ciloleucel infusion.

ADVERSE EFFECTS

Besides the great response, CART cell therapy have some adverse effects like Cytokine Release Syndrome, Neurologic toxicities, Hypersensitivity reactions, Serious infections, Prolonged Cytopenias and Hypogammaglobulinemia. Among this Cytokine Release Syndrome (tumor lysis syndrome) is a life-threatening ADR in which interleukin-6 plays a major role[15]. But this can be managed with Tocilizumab (an immunosuppressant drug that will inhibit the proinflammatory effects of soluble and membrane bound interleukin-6) and corticosteroid[9,12].

CURRENTLY ACTIVE STUDIES

Currently 328 studies are going on to evaluate the safety and efficacy of CART cell in cancer[16]. Among that few studies to evaluate the safety and efficacy of Tisagenlecleucel and Axicabtagene Ciloleucel are:

- ✓ Study of efficacy and safety of CTL019 in pediatric ALL patients (clinical trial.gov. identifier- NCT02228096).
- ✓ A phase I/II multicenter study evaluating Axicabtagene Ciloleucel in subjects with Refractory Aggressive Non-Hodkin Lymphoma (ZUMA 1 trial: clinical trial.gov. identifier- NCT02348216).
- ✓ Determine efficacy and safety of CTL019 in pediatric patients with relapsed and refractory B cell ALL (ELIANA trail: clinical trial.gov. identifier- NCT02435849).

- ✓ Study of efficacy and safety of CTL019 in adult DLBCL patients (JULIET trail: clinical trial.gov. identifier-NCT02445248).

In the light of recent FDA approval and various ongoing studies, CART cell gives a great hope in cancer treatment where it is refractory/ relapse to conventional therapy.

CONCLUSION

CART cell therapy holds tremendous potential for cancer cure, and researches are on the way exploring the application of CART cell therapy in the treatment of solid tumors.

If the results of ongoing studies became positive then CART cell therapy- Tisagenlecleucel and Axicabtagene Ciloleucel- approved by US FDA in 2017 can be considered as the near miracle cure for Cancer.

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