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Novel approach to treat lymphoblastic leukemia "Kymriah" and its scope in India

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Acute lymphoblastic leukemia is a type of cancer which occurs when a bone marrow cell develops errors in its DNA and affects the white blood cells. Kymriah is first FDA approved gene therapy which treats B-cell acute lymphoblastic leukemia (ALL) in patients aged 25 years and younger. It is used in patients whose cancer has relapsed or is refractory. It is formulated in-vivo using a patient's T cells and a gene, code for a special receptor called chimeric antigen receptor (CAR). It is reprogrammed to destroy cancerous B-cell and is administered by IV infusion. Tisagenlecleucel is a CD19-directed genetically modified autologous T cell immunotherapy marketed as Kymriah by Novartis. The whole process takes 22 days as the T cells from a person with cancer are removed, genetically engineered to make a specific T-cell that reacts to cancer, and transferred back to the person. It was invented and initially developed at the University of Pennsylvania; Novartis completed development, obtained FDA approval, and markets the treatment. In August 2017, it became the first FDA-approved treatment that included a gene therapy step in the United States. It is administered in a single treatment, which will have high cost, if not successful money is refunded. Present study highlight first gene therapy based "LIVE" treatment for lymphoblastic leukemia and conducts a survey on knowing the attitude of Indian population towards gene therapy to understand the scope of Kymriah in India.

Keywords: Kymriah, lymphoblastic leukemia, Tisagenlecleucel, Gene therapy

Introduction

Tisagenlecleucel marketed as Kymriah is a treatment for B-cell acute lymphoblastic leukemia which uses the body's own T cells to fight cancer. Kymriah is a genetically modified autologous T-cell immunotherapy. Each of its doses is a tailored treatment created using an individual patient's own T-cells, a type of white blood cell known as a lymphocyte. It is used to treat acute lymphoblastic leukemia which has been relapsed or in the refractory stage.

T cells from a patient suffering from cancer are removed, genetically engineered to make a specific T-cell receptor that reacts to the cancer, and transferred back to the person. The T cells are programmed to target a protein called CD19 that is common on B cells. A chimeric T cell receptor ("CAR-T") is expressed on the surface of the T cell. It was invented and earlier developed at the University of Pennsylvania after that Novartis completed development, obtained FDA approval, and marketed the treatment. In August 2017, it became the first FDA-approved chimeric treatment that included a gene therapy step in the United States. [1]

In this study, we draw special attention to first gene therapy based "LIVE" treatment for lymphoblastic leukemia and conduct a survey on knowing the attitude of Indian population towards gene therapy to understand the scope of Kymriah in India.

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Methodology

This study was divided in two parts 1. Generation of literature based data 2. Questionaire based survey. Literature based searched was done using online databases Medline, Pub Med from NCBI and Google scholar to know the awareness about first gene therapy based "LIVE" treatment for lymphoblastic leukemia. The keywords Kymriah, lymphoblastic leukemia, Tisagenlecleucel etc. were used for searching. Furthermore, a questionnaire based survey was conducted on knowing the attitude of Indian population towards gene therapy to understand the scope of Kymriah in India. So, a customised questionnaire was prepared and survey was conducted on healthy volunteers (n= 250) in including male and female in 20 to 50 years about knowing the attitude of Indian population about gene therapy "KYMRIAH".

History of Therapy Development

This treatment was developed by a group headed by Carl H. June at the University of Pennsylvania and is licensed to Novartis. In August 2017, Kymriah (CTL019) received get through therapy designation by the US FDA for the treatment of relapsed or refractory diffuse large B-cell lymphoma.This treatment will be administered at specific medical centers where staff has been highly trained to manage possible side effects to this new type of treatment.[2]

Acute lymphoblastic leukemia

Adult acute lymphoblastic leukemia (ALL) is a form of cancer in which the bone marrow makes too many lymphocytes. Leukemia may affect red blood cells, white blood cells, and platelets.

Occurs fewer than 1 million cases per year (India).Acute lymphoblastic leukemia is the most common childhood cancer. It occurs when a bone marrow cell develops errors in its DNA making abnormal amount of WBC. Symptoms are enlarged lymph nodes, fever, bone pain, bruising, bleeding from the gums and frequent infections.[3]

Acute Lymphoblastic Leukemia can be of B- cell or T-cell origin. B-cell precursor. ALL in paediatric and young adult patients is characterised by a common antigen on the membrane of the cell in the majority of cases, not only at initial diagnosis, but also at relapse. This antigen is called CD19. About 80-85% of paediatric ALL diagnosis are B-cell precursor in origin and CD19 positive.

CD19 Expression is restricted to B lineage cells and is not expressed by any pluripotent blood stem cells. Since CD19 is present only to B cell, the effect of an anti-CD19 agent would chiefly affect B-cell function. CD19 is expressed by B-cell malignancies in particular B-cell precursor ALL. This made CD19 a natural target for immunotherapy. [4]

The strategy with tisagenlecleucei was to produce genetically engineered chimeric antigen receptor (CAR) T cells transfixed with chimeric receptor genes to combine the effectors functions of T lymphocytes with the ability of antibodies to recognize predefined surface antigens with high specificity in a non-MHC restricted manner. The target was CD19 on the surface of the B-cell precursor blasts. Paediatric and Young Adult B-cell Precursor Acute Lymphoblastic Leukemia Acute lymphoblastic leukemia (ALL) occurs in children and adults.[1]

Mechanism of Action

KYMRIAH is a customised therapy that reprograms a patient's own T cells with a chimeric antigen receptor (CAR) containing a 4-1BB co stimulatory domain. The 4-1BB co stimulatory domain is responsible for enhancing the expansion and persistence of KYMRIAH.

The KYMRIAH CAR also contains a CD3? intracellular signalling domain, which is important for initiating T-cell activation and antitumor activity. [6]

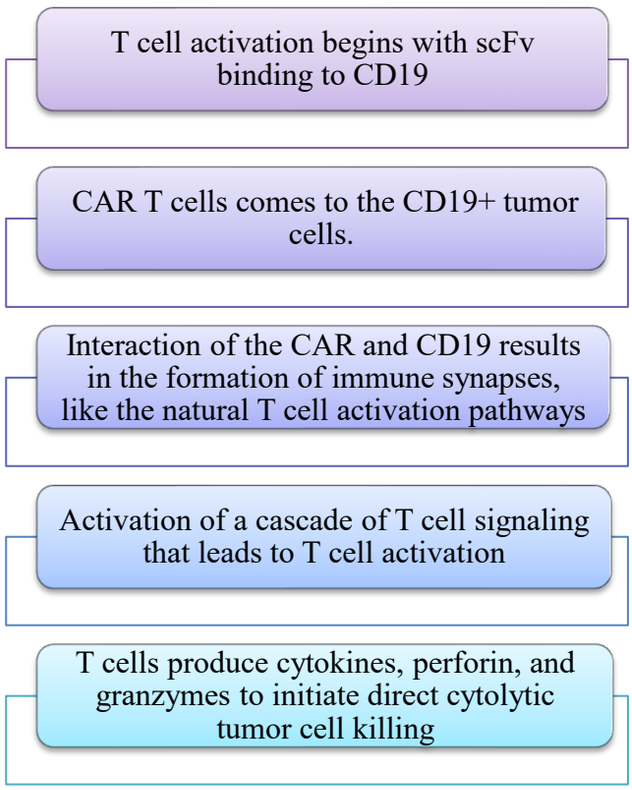

Figure 1 : Mechanism of action is the direct cytolytic killing of tumour cells.

Product Description

KYMRIAH is composed of autologous T cells that are genetically modified with a lenti-viral vector which encodes a chimeric antigen receptor (CAR). The CAR specifically recognizes the CD19 protein present on CD19+ B lineage tumour cells as well as normal B cells.

Dosage and Half Life

KYMRIAH is given in a single-dose unit containing chimeric antigen receptor (CAR)-positive viable T cells based on the patient weight which is reported at the time of leukapheresis. For patients 50 kg or less: administer 0.2 to 5.0 x 106 CAR-positive viable T cells per kg body weight. For patients above 50 kg: administer 0.1 to 2.5 x 108 CAR-positive viable T cells. The mean half-life was 16.8 days in paediatric and young adult relapsed/refractory B-cell acute lymphoblastic leukemia (ALL) patients. [7]

Clinical Pharmacology

KYMRIAH displayed an initial quick expansion phase achieving maximal concentration (Cmax) around day 10 followed by a slower bi-exponential decline in complete remission/complete remission with incomplete hematologic recovery (CR/CRi) patients on day 28.

Cmax and AUC0-28d of KYMRIAH were higher in CR/CRi patients as compared with non-response patients.

No difference in the pharmacokinetics of KYMRIAH was noted for gender and different race. Children, less than 10 years of age have higher Cmax and AUC about 1.5 to 2-fold higher than adults. Both Cmax and AUC0-28d decreased with increasing age. However, due to small sample size and high variability, it was difficult to evaluate a definitive impact of age on the PK of KYMRIAH. [7]

Efficacy

Approval of the treatment was based on a single-arm trial of 63 paediatric patients with precursor B-cell ALL.3 Patients received a single dose of tisagenlecleucel intravenously within 2 to 14 days following completion of lymphodepleting chemotherapy of fludarabine and cyclophosphamide.

The confirmed overall remission rate at 3 months was 82.5% (95% confidence interval [CI], 70.9-91.0), which is significantly higher than the alternatives.

Storage Condition: Kymriah comes from the manufacturer as a frozen suspension. It should be stored in the vapour phase of liquid nitrogen at less than or equal to -120 °C.[8]

Lab to Patient: Product Delivery

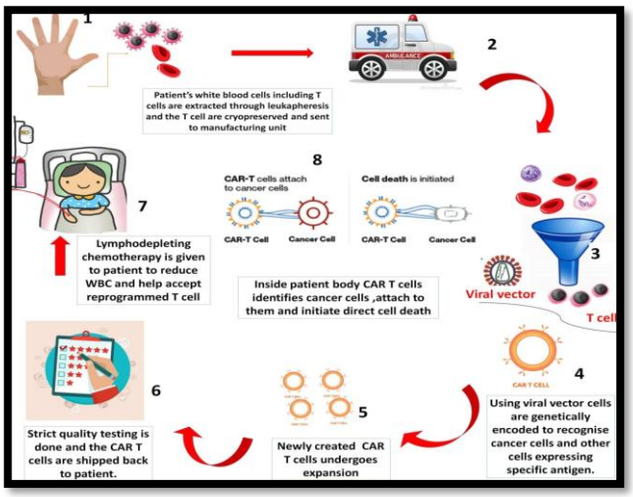

Figure 2: Shows that all steps involves in preparation from lab processing to patient delivery

Steps involved in Processing of Product

- **Blood Filtering**

At the hospital, the patient's immune T cell is taken from the blood, frozen and transported to the Novartis plant.

- **Reprogramming**

It genetically programs the T cells to recognise a distinctive marker on B cells which turn malignant for leukemia.

- **Expansion**

The modified T cells are multiplied for over 3- 4 weeks, frozen and shipped back to the hospital for the patient.

- **Preparing The Patient**

The patient gets some chemotherapy to kill some white blood cells and help the body to accept the modified T cell.

- **Infusion**

The modified T cells are infused back into the patient's vein.

- **Attacking The Cancer**

The T cells attack on the malignant B cells and kill cancer. [6]

Inclusion criteria for Kymriah: Patients are applicable for KYMRIAH if

They have not gone into remission following frontline treatment (primary refractory)

Have relapsed and cannot achieve remission (chemo refractory)

Have had second or subsequent relapse after complete remission or stem cell transplant (SCT)

Monitoring:

- **Short-term monitoring**

Patients should stay within 2 hours of their KYMRIAH Treatment Center for at least 4 weeks after infusion to monitor for, and treat, potential side effects. Caregivers should also remain with the patient to check for signs of fever or other side effects.

- **Long-term monitoring**

Routine long-term monitoring is required for potential secondary malignancies. Patients should be informed about, and encouraged to participate in, the KYMRIAH registry. [9]

Cost for Magic Life Saving Therapy

It is Single dosage administered treatment, which will cost $475,000. Novartis says that this treatment is cheaper than some bone marrow transplants. Novartis will not charge patients who have not responded to the treatment. [10]

Side Effects

Cytokine release syndrome (CRS), which is a systemic response to the activation and proliferation of CAR T-cells causing very high fever and flu-like signs, and for neurological events

Low blood pressure (hypotension)

Acute kidney injury

Fever and decreased oxygen (hypoxia) [6]

Survey Results: Results are summarized in Figure 3 and 4.

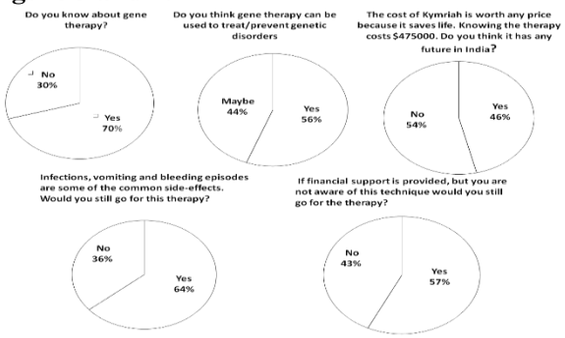

Figure 3: Shows survey responses in population with age 20-50 Years in 250 subjects including male and female resident of NCR.

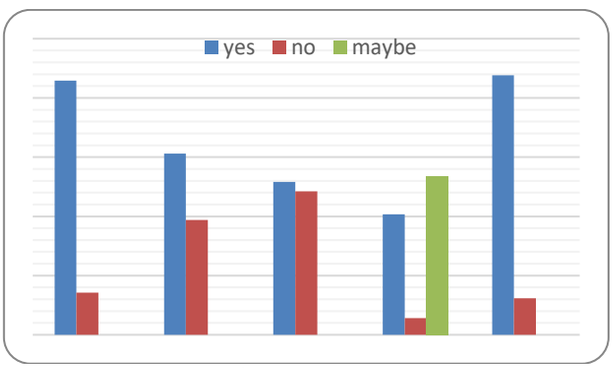

Figure 4: Shows survey responses

Conclusion

This ground breaking customize treatment of curing cancer has a lot of potential in treating the patient suffering from leukemia. This treatment has shown a massive response rate in people with these cancers. It's given hope to patients and parents. If other treatments fail, they can go for this drug that teaches our cells to fight cancer. This treatment should also be approved in India as its cost is comparably less and effective than other treatments. From the survey conducted most respondents about 70% indicated prior knowledge about gene therapy; the proportion responded considering gene therapy is high as 88% which is quite good and for genetic enhancement. Concern for side effects is very less. And acceptability of Kymriah as per Indian scenario is also good. So, we can say that if this treatment is brought to India it will have a success rate higher than expected.

References

1. Us.kymriah.com.Understanding Pediatric ALL Treatment | KYMRIAH® (tisagenlecleucel). [online] Available at: https://www.us.kymriah.com/acute-lymphoblastic-leukemia-children/about-treatment/understanding-treatment/.
2. Healthcare, G. and Healthcare, G. (2018). The world's first CAR-T therapy has been approved for a second indication. Pharmaceutical Technology. Available at: https://www.pharmaceutical-technology.com/comment/worlds-first-car-t-therapy-approved-second-indication/
3. Cancer.org. What Is Acute Lymphocytic Leukemia (ALL)? | Acute Lymphocytic Leukemia (ALL). [online] Available at: https://www.cancer.org/cancer/acute-lymphocytic-leukemia/about/what-is-all.html.
4. National Cancer Institute.Childhood Acute Lymphoblastic Leukemia Treatment. [online] Availableat:https://www.cancer.gov/types/leukemia/patient/child-all-treatment-pdq#section/all.
5. Fda.gov.(2018).[online]Availableat:https://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM573941.pdf.
6. Us.kymriah.com. Understanding Pediatric ALL Treatment | KYMRIAH® (tisagenlecleucel). [online] Availableat:https://www.us.kymriah.com/acute-lymphoblastic-leukemia-children/about-treatment/understanding-treatment/.
7. Reference.medscape.com. (2018). Kymriah

(tisagenlecleucel) dosing, indications, interactions, adverse effects, and more. [online] Available at: https://reference.medscape.com/drug/kymriah-tisagenlecleucel-1000169.
8. Hcp.novartis.com. (2018). KYMRIAH® (tisagenlecleucel) Efficacy Data & Clinical Trials | HCP. [online] Available at: https://www.hcp.novartis.com/products/kymriah/diffuse-large-b-cell-lymphoma-adults/efficacy/
9. Hcp.novartis.com. (2018). KYMRIAH Treatment Process, Dosing & Administration | HCP. [online] Available at: https://www.hcp.novartis.com/products/kymriah/acute-lymphoblastic-leukemia-children/dosing-and-administration/
10. Staines, R. (2018). Novartis matches Gilead on price in new CAR-T use - Pharmaphorum. [online] Pharmaphorum. Available at: https://pharmaphorum.com/news/novartis-matches-gilead-kymriah/