CAR T CELLS – GET OWN CELLS TO TREAT CANCERS

Recently, sitting in my TV lounge, I watched a footage on BBC: a living drug for childhood blood cancers, has an 87% cure rate, comes with a price tag of $475,000 per patient, and has been approved by FDA. The drug consists of patient's OWN T cells, armed *in vitro* to attack and kill the cancer cells after being infused back to the same patient.

As a student of Immunology, reading passages on passive immunity, I always wondered how adoptive transfer of cells could be a worthwhile medium of passive immunity…neutrophils have such a short life in circulation and foreign lymphocytes would be readily attacked and eliminated by the host immune system. Just another theoretical mess to irritate students. But, here we are, with amazing possibilities!

Classical treatments for cancers remind us of surgery, chemotherapy, and radiation therapy. In the last two decades, targeted therapies like imatinib (Gleevec®) and trastuzumab (Herceptin®)—drugs that target cancer cells—have established themselves as standard treatments for some cancers. Now, the world is likely to witness the miracle of immunotherapy—therapies that tap the power of a patient's immune system to attack tumours—as the "fifth pillar" of cancer treatment.

A rapidly emerging immunotherapy approach called adoptive cell transfer (ACT), collecting and using patients' own immune cells to treat their cancer can employ various theoretical means but, thus far, the one that has advanced the furthest in clinical development is CAR (Chimeric Antigen Receptor) T-cell therapy. Initially used for advanced blood cancers, the treatment offers great hope for both children and adults when all other treatments had stopped working. Last year, Food and Drug Administration (FDA) approved two CAR T-cell therapies, one for the treatment of children with acute lymphoblastic leukemia (ALL) and the other for adults with advanced lymphomas.

As its name implies, the backbone of CAR T-cell therapy is T cells, which are often called the workhorses of the immune system because of their critical role in orchestrating the immune response and killing cells infected by pathogens. The therapy requires drawing blood from patients and separating out the T cells. Next, using a disarmed virus, the T cells are genetically engineered to produce receptors on their surface called chimeric antigen receptors, or CARs. These receptors are synthetic molecules, don't exist naturally and allow the T cells to recognize and attach to a specific protein, or antigen, on tumour cells. The CAR T cell therapies target an antigen found on B cells called CD19. Once the collected T cells have been engineered to express the antigen-specific CAR, they are "expanded" in the laboratory into the hundreds of millions. The final step is the infusion of the CAR T cells into the patient (which is preceded by a "lymphodepleting" chemotherapy regimen). If all goes as planned, the engineered cells further multiply in the patient's body and, with guidance from their engineered receptor, recognize and kill cancer cells that harbour the antigen on their surfaces.

The progress made with CAR T-cell therapy in children with ALL has been fantastic and the results in lymphoma to date have been termed incredibly successful. There are cohorts of patients, who would have been considered terminal, but are now in durable and meaningful remissions with good quality of life for up to 5 years,

CAR T-cell therapy can cause several worrisome, and sometimes fatal, side effects. One of the most frequent is cytokine release syndrome (CRS). T cells release cytokines, chemical messengers that help to stimulate and direct the immune response. A rapid and massive release of cytokines into the bloodstream can lead to dangerously high fevers and precipitous drops in blood pressure. In many patients, CRS can be managed with standard supportive therapies, including steroids. In more serious cases of CRS, blockade of IL-6 is the key to treatment.

Another potential side effect of CAR T-cell therapy—an off-target effect—is a mass die off of B cells, known as B-cell aplasia. Normal B cells are also often killed by the infused CAR T cells. To compensate, many patients must receive immunoglobulin therapy, which provides them with the necessary antibodies to fight off infections.

One might wonder: what is next! Imagined and real future developments include preparing CAR T cells not from the actual patients but from healthy donors. These ready-made cells would be available immediately like other drugs and don't have to be actually prepared for individual patients. Other novel methods are *in vivo* preparation of CAR T cells (inside the body) by nanotechnology, making cells

with “off switches” to minimize the side effects and using gene editing technology to precisely engineer the T cells.

The potential and the possibilities are endless and magical but human desires and imagination, the driving force for all possibilities to take form, far exceed everything, as Ghalib said it so well:

ہے کہاں تمنّا کا دوسرا قدم یا رب
ہم نے دشتِ امکاں کو ایک نقشِ پا پایا

Where will the next step of desire be, O Lord,
I/ we found the whole desert of possibility to be just one footprint.

REFERENCES

1. CAR T Cells: Engineering Patients’ Immune Cells to Treat Their Cancers (originally published by the National Cancer Institute, USA)
2. Abbas AK, Lichtman AH, Pillai S. Cellualar and molecular immunology. Ninth Edition. Elsevier Saunders. 2018; 410-2.

Brig Mukarram Bashir
MBBS, FCPS,
Deputy Commandant (Technical)
Head of the Department of Immunology
Armed Forces Institute of Pathology
Rawalpindi, Pakistan
Email: mmb6262@hotmail.com