

Chimeric Antigen Receptor (CAR) T-cell therapy; a promising outlook for refractory malignancies

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Madam, today, adults with relapsed or refractory B-cell malignancies continue to have poor prognosis despite significant treatment advances.¹ CAR T-cell therapy is a new treatment approach under investigation for these patients. B-cell malignancies express specific tumour associated antigens including CD19. T-cells can be genetically engineered to express a chimeric antigen receptor (CAR) that recognizes the B-cell antigen CD19.² CD19 is expressed on developing and mature B-cells, absent on pluripotent haematopoietic stem cells and highly retained over the process of neoplastic transformation. CARs are recombinant receptors that redirect T-cell specificity to target a tumour associated antigen in an HLA independent manner.³ CAR T-cell therapies having been recently approved by the FDA are still a budding feat. As of yet the therapy has limited indications and the approval is namely for Acute Lymphoblastic Leukaemia (ALL) and Non Hodgkin's Lymphoma NHL but there is a promise of thriving further.

CAR T-cell therapies contain a mixture of CD4 and CD8 cells. It begins with the collection of each patient's T-cells. The patient's blood is separated through leukopheresis and the PBMC fraction containing the lymphocytes is collected.⁴ The (CAR) that will be inserted into the activated cells is a recombinant receptor composed of a targeting domain or extracellular antigen recognition that is linked via spacer hinge and transmembrane domains to an intracellular signaling domain. DNA encoding this construct can be transduced ex-vivo using transfection gamma retroviral or lentiviral recombinant vectors or a transposon system. The engineered T-cells may continue to multiply differentiate into memory cells and live in the body potentially establishing immune memory.

Prior to infusion, patients will receive conditioning

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with lympho-depleting chemotherapy to improve persistence of their CAR T-cells.¹ Upon binding with its targeted antigen, the CAR initiates signaling and activation of the T-cell by undergoing a conformational change that transmits the binding signal through the cell membrane and into the cell. Activated CAR T-cells release perforin and granzymes that attack tumour cells directly. Activation may result in the release of cytokines and transcription factors that promote T-cell survival and trigger apoptosis in the tumour cell.

Currently, the therapy is a beacon of hope in the fight against cancer in developed countries. However, in developing countries like Pakistan, due to scarce funding the therapy remains a matter of contention. A single treatment cost for treating could run hundreds of thousands of dollars with estimates as high as \$500,000 to \$750,000 (Rs55Million-Rs83Million).

Further research needs to be done to counter the detrimental side effects including very high fevers and dangerously low blood pressure days after treatment. This phenomenon is known as Cytokine Release Syndrome or CRS. Other serious toxicities include Neurotoxicity or changes in the brain that would result in confusion, seizure or severe headaches. Trials have also reported development of serious infections, low blood cell counts, immunosuppression and B-cell aplasia. Therefore, these toxicities must be promptly reported as they may require immediate medical attention from the cancer care team and if overlooked may even result in death.

A country like Pakistan, where incidence of NHL is mounting,⁵ must embrace this form of innovative technology with enthusiasm. This letter resolves to get the conversation for CAR T-cell therapy started in Pakistan as with appropriate health reforms and government funding, regardless of its limitations, this new approach holds remarkable potential for many patients with previously incurable malignancies.

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