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Editorial

T-cell transfer therapy: A primer

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T-cell transfer therapy is a process of immunotherapy that has generated substantial interest in recent years. Monoclonal antibodies (mAbs) have, for some time, dominated the scene of immunotherapy for treating cancers as they can be designed in laboratories in such a way as to target a specific antigen of the tumor cell.[1] MAbs are used both in the treatment of solid tumors as well as leukemias. Trastuzumab (Herceptin) the antibody against the HER2 protein is widely used in HER2+ breast carcinomas. Rituximab, which binds to a protein called CD20 on B cells, is used to treat CD20-positive B-cell Non-Hodgkin's Lymphoma (NHL), chronic lymphocytic leukemia (CLL) etc.

In the last decade or so, immune-checkpoint inhibitors (ICI) came into the limelight. They are targeted mAbs working against molecules like the programmed cell death-1 (PD-1), its ligands (PDL1/PDL2), or cytotoxic T lymphocyte antigen 4 (CTLA-4) which are present either on the tumor-infiltrating lymphocytes (TILs) or on the surface of the tumor cells of some cancers.[2,3] ICIs like pembrolizumab, atezolizumab, durvalumab, and avelumab have now shown promising results in many cancer types.[2]

T cell transfer therapy is a form of Adoptive Cell Therapy (ACT) that involves the isolation of a patient's T cells followed by modification and multiplication of those cells in the laboratory. These cells are then re-introduced into the patient's circulation.[3] Thus, this is a process of artificially strengthening one's own immune cells to fight against his/her cancer.

This processing of T cells in the laboratory may take 2 to 8 weeks.[4] During this time, the patient is subjected to nonmyeloablative lymphodepletion by chemotherapy and radiation therapy so that there is less chance of reaction against the reinjected T cells.[4]

T-cell transfer therapy can be divided into 2 major types:

1. TIL therapy
2. CAR T-cell therapy

TIL Therapy

Tumor-infiltrating lymphocytes (TILs) are naturally occurring lymphocytes that infiltrate the solid tumor microenvironment (TME).[5] A high baseline TIL density has been reported to be associated with improved outcomes in several solid tumors that have been treated with immune checkpoint inhibitors including melanoma, endometrial cancer, breast cancer, colorectal cancers, and non-small cell lung carcinomas.[6] Now, this TIL is being used as a potential therapy for several cancers.

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The major steps of TIL therapy, as nicely illustrated by Kasemi et al,[5] are:

1. Isolation of TILs from resected tumor tissue - excision of tumor→ cutting of the tissue into small pieces→ enzymatic digestion by collagenases, DNAse, hyaluronidase etc→ isolation by Ficoll density gradient centrifugation/ magnetic- or fluorescence-activated cell sorting (MACS/FACS)
2. Expansion of TILs ex vivo [primary expansion in the presence of high-dose interleukin-2 (IL-2) for 2-5 weeks (pre-REP phase) which causes rapid proliferation of lymphocytes→ rapid expansion protocol (REP) for 2 weeks in which high dose IL-2, anti-CD3 are added to the TILs and irradiated allogeneic peripheral blood mononuclear cells (PBMCs) are also added as feeder cells→ expanded T cell population is subjected to quality control checks]
3. Nonmyeloablative lymphodepletion of the patient 7 days prior to TIL administration by fludarabine and cyclophosphamide
4. TIL administration: 10-150 billion TILs that have passed the quality checks for blood-borne diseases, sterility, and phenotype are infused intravenously into the patient along with a high dose of IL-2.

TIL therapy has shown significant clinical results in metastatic melanoma,[7] squamous cell carcinoma of the cervix,[8,9] and cholangiocarcinoma.[10] The initial results in non-small cell lung cancer (NSCLC), colorectal cancer (CRC), and HR (Hormone receptor) positive breast cancer have been encouraging.[11–14]

A recognized side effect of TIL therapy is capillary leak syndrome (CLS). This syndrome results in plasma and protein leakage out of tiny blood vessels causing hypotension, and hypoalbuminemia. It may even lead to multiple organ failure and shock.[4]

CAR-T Cell Therapy

CAR stands for chimeric antigen receptor. CAR-T cell therapy is similar to TIL therapy, only the T cells are modified in the laboratory so that they can attack the cancer cells by attaching to specific proteins on the surface of the cancer cells.

The major steps include:[15]

1. Leukapheresis in which the white blood cells (which include T cells) are removed from the patient's blood (autologous) or from a donor (allogenic) → purification of T cells.
2. T cells are genetically engineered to express a special receptor known as chimeric antigen receptor (CAR) by transducing the patient's T cells with a virus.[16]
3. Expansion of the number of CAR-T cells in the laboratory.
4. Nonmyeloablative lymphodepletion.
5. Infusion of CAR-T cells into the patient. This CAR will bind to a certain protein, the tumor-associated antigen (TAA) on the cancer cell. Following the binding, the CAR-T cells get activated, proliferate and finally destroy the cancer cells that carry that specific antigen.

In 2017, FDA approved the first CAR T-cell therapy against B-cell acute lymphoblastic leukemia (ALL) in children followed by diffuse large B-cell lymphoma and certain other types of lymphoma in 2018.[2]

The 6 FDA approved CAR T-cell therapies for blood cancers are:[15]

1. Axicabtagene ciloleucel
2. Brexucabtagene autoleucel
3. lisocabtagene maraleucel
4. Tisagenlecleucel
5. Ciltacabtagene autoleucel
6. Idecabtagene vicleucel

Other than leukemia/lymphoma and multiple myeloma, there are ongoing clinical trials on the effect of CAR-T cell therapy on various types of solid tumors like cancers of the pancreas, prostate, breast, thyroid, brain etc.[16]

In spite of its promising results, the CAR-T therapy has serious often life-threatening complications like Cytokine Release Syndrome (CRS), neurologic toxicity, low blood counts, allergic reaction etc.[15] CRS is a systemic inflammatory response caused by the release of large amounts of cytokines caused by proliferating infused CAR T cells leading to widespread reversible organ dysfunction.[17]

To conclude, T cell transfer therapy is a form of immunotherapy which has shown promising results in various types of malignancies ranging from solid cancers to leukemias. In cases that do not respond to treatment, alternative therapeutic strategies using combination therapies are followed. High cost and serious side effects are major hindrances to their widespread use. However, with more and more clinical trials on the way, T-cell transfer therapy will show its beneficial role in many cancers in the near future.

Conflict of Interest

None.

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