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Perspective

Chimeric antigen T cell receptor treatment in hematological malignancies

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The treatment of malignant hematological disorders is still challenging, particularly in cases of refractory diseases. Although hematopoietic stem cell transplantation is a potentially curative option, it has been associated with a transplant-related mortality rate of 20–25% [1]. The technique of adoptive T cell transfer has gained significant focus in the field of hematology in recent years. Chimeric antigen receptor T cell (CAR-T cell) therapy is a novel immunotherapy technique in which T lymphocytes are engineered with synthetic receptors known as the chimeric antigen receptors (CAR). This engineered effector CAR-T cell is capable of recognizing and eliminating cancer cells. It performs this function independent of the major histocompatibility molecules. CAR-T cell therapy is being used for the treatment of hematological malignancies, such as acute lymphoblastic leukemia, acute myeloid leukemia, lymphomas, and multiple myeloma.

With the advent of the use of retroviral vectors and T cell engineering, the first generation of CAR-T cells was developed in 1990 [2]. Due to their short half-life, the first generation of CAR-T cells was not very efficacious. However, almost a decade later, a co-stimulatory domain was developed, which set forth the development of second generation CAR-T cells and eventually, in 2003, a product targeting CD19 was developed [3]. In 2011, these CAR-T cells were successfully used in a patient with acute lymphoblastic leukemia. Currently, two therapies of US Food and Drug Administration (FDA) approved CAR-T cells are available, which include the use of axicabtagene ciloleucel (KTE-C19) and tisagenlecleucel (CTL019) [4]. Axicabtagene ciloleucel and tisagenlecleucel have been approved for relapsed/refractory conditions of Non-Hodgkin's lymphoma in young adults and B-acute lymphoblastic leukemia in pediatric and adult patients, respectively. The most recent data obtained from the ZUMA-1 study presented at the American Society of Clinical Oncology in 2018 showed that, after therapy, a complete response rate of 58% at 15.1 months was observed in patients with diffuse large B-cell lymphoma [5]. The efficacy data of the phase II single-arm study on tisagenlecleucel showed that a complete remission had occurred in 93% and 58% of patients at one month and twelve months, respectively [6].

Another ideal chimeric receptor antigen that has been focused upon in recent times for the treatment of multiple myeloma is the B cell maturation antigen (BCMA). BCMA or CD269 is the seventeenth member of the tumor necrosis factor superfamily (TNFRSF17) [7]. The main role of BCMA is to regulate B cell maturation and survival during their differentiation into plasma cells. It is ubiquitously expressed on members of the B cell lineages, which include plasmablasts and plasma cells, but not on hematopoietic stem cells and naïve B cells. In 2016, Kochenderfer *et al.* [8] reported the results of the first clinical trial conducted on humans on the safety and efficacy of second generation anti-BCMA-CAR with CD3/CD28 signaling domains. Twelve patients were enrolled in the study and received a single dose of CAR-BCMA T cells, which was subsequently escalated for four levels as follows: 0.3, 1, 3, and 9×10^6 CAR-T cells/kg body weight. Effective clinical responses

were seen at higher dose levels (3 and 9×10^6 cells/kg). This trial provided evidence on the anti-myeloma activity of CAR-BCMA cells and opened avenues for subsequent trials to employ immunotherapy as a treatment option for multiple myeloma.

Based on the successful outcome of CAR-T cell therapy for B cell malignancies, various groups started working on cellular or antibody-based immunotherapies for acute myeloid leukemia (AML). The CD33 antigen, which is expressed on healthy myeloid and myeloid progenitor cells with 90% expression in myeloid leukemic blast cells, is a potential target for these immunotherapies. This antigen has been targeted previously when a humanized drug-conjugated anti-CD33 antibody (Gemtuzumab) was developed and approved by FDA in 2000 [9]. In 2010, it was withdrawn from the European and US markets due to resulting complications of bone marrow toxicity and veno-occlusive disease. However, it was reintroduced in 2018, after Hills *et al.* [10] published a meta-analysis suggesting that a low fractionated dose of Gemtuzumab in combination with chemotherapy had improved overall survival in patients with AML. Because of this response and the increased expression of CD33 on myeloid cells, many clinical trials are underway on anti-CD33 CAR therapy.

There has been considerable progress on the application of CAR-T cell therapy in recent decades, although, with associated toxicities. The maximum toxicity is observed in the cytokine release syndrome (CRS) associated with anti-tumor activity in which the patients may develop symptoms such as high-grade fever, hypoxia, hypotension or mild flu [11]. Another complication associated with this is the tumor lysis syndrome caused due to a rapid and massive destruction of cancer cells [12]. The macrophage activation syndrome is another life threatening complication resulting in systemic inflammatory response and pancytopenia with an unknown mechanism of action [13].

In order to decrease the toxicities associated with this therapy, the patients must undergo a thorough physical evaluation and its profile should include an assessment of cardiac function, bone marrow examination and graft versus host disease status. Tumor lysis protocol is started preemptively in patients with bulky disease. At the time of infusion, aggressive hemodynamic assessment and supportive care should be carried out by evaluating complete blood counts, metabolic panel, and markers for tumor lysis. Cytopenias resulting from CAR-T cell infusion can be managed with transfusion support and administration of growth factor. For the cytokine release syndrome, Tocilizumab (IL-6 receptor antagonist) is being used extensively as an off-label therapy in patients who have developed this catastrophic complication [14]. Other therapies for the treatment of CRS include the use of corticosteroids, siltuximab and etanercept.

The use of CAR-T cell therapy is the future in the treatment of hematological malignancies. Currently their role is limited to a refractory/relapsed setting but soon this option will be incorporated in treatment paradigms at multiple points. Adverse events include the development of CRS, which is still a challenge preventing its widespread use. Cutting-edge bench research is required to improve the effectiveness of this therapy that can provide physicians and patients a better chance at eradicating hematological cancers.

Authors' Disclosures of Potential Conflict of Interest

No potential conflict of interests relevant to article were reported.

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