Chimeric Antigen Receptor (CAR) T-Cell Therapy And Cytokine Release Syndrome: Do We Need To Be Innovative To Overcome The CAR T-Cell Associated Toxicities

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Abstract

Chimeric antigen receptor (CAR) T -cell therapy is the target specific therapy that utilizes the function of genetically engineered T -cells in production of artificial T-cell receptors for being utilized as immunotherapy for treating cancers. It's not only an exciting revolution in the field of hematology, but also now being utilized in treatment of solid tumors. Despite of having such an exciting revolution, the use of CAR T-cell therapy is restricted due to its associated toxicities like cytokine release syndrome (CRS) and neurotoxicity thus posing the dire need of development of new strategies that could ameliorate the toxic side effects and can provide better target specific therapies like CAR off switches, suicide gene strategies, modifying the CAR transduced T cells, and altering the affinity of the CAR -T cell's antigen binding domain.

Keywords: CAR-T cell therapy, Cytokine release syndrome, Toxicity.

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Chimeric antigen receptor (CAR) T-cell therapy is the target specific therapy that utilizes the function of genetically engineered T-cells in production of artificial T-cell receptors for being utilized as immunotherapy for treating cancers.[1] The genetically engineered T-cells formed through CAR-T cell therapy are destined to act on specific targets in order to achieve heroic therapeutic results in treatment of various cancers.[1] Chimeric antigen receptor (CAR)-T cell therapy has been revolutionary as it has produced remarkably effective and durable clinical responses. CARs are engineered synthetic receptors that function to redirect lymphocytes, most commonly T cells, to recognize and eliminate cells expressing a specific target antigen. CAR binding to target antigens expressed on the cell surface is independent from the MHC receptor resulting in vigorous T cell activation and powerful antitumor responses.[2] Tisagenlecleucel (Kymriah®) was the first Chimeric antigen receptor T-cell therapy that was approved by the US Food and Drug Administration (FDA) in 2017 for being utilized in treatment of B-cell acute lymphoblastic leukemia in children and young adults.[2] There are many other newly developed CAR T cells therapies like Axicabtagene Ciloleucel (Yescarta®), Idecabtagene vicleucel (Abecma®), Lisocabtagene maraleucel (Breyanzi®) that are now being excitingly utilized in the treatment of various hematological malignancies like mental cell lymphoma, multiple myeloma, and large B-cell lymphoma.[3] The utilization of CAR T cell therapy is now being a matter of debate for being used for solid tumors as well.

Despite of being highly effective therapy in treatment of B-cell ALL with 81% response rate, improvement in overall survival (OS) and progression free survival (PFS), and being excellent in other malignancies, there are some limitations that have been observed in patients undergoing CAR-T cell therapy. The most commonly observed limitations are antigenic escape, on target off tumor, CAR T-cells trafficking and infiltration, immunosuppressive microenvironment and finally the CAR-T cell therapy associated toxicities.[4] The most common and lethal of all toxicities was cytokine release syndrome along with neurotoxicity observed in patients undergoing CAR T-cell therapy.[5] Although CAR T-cell therapy has been approved as a revolutionary step towards the field of oncology, still the CAR T-cell therapy associated toxicities have been preventing it to be used as first line therapy. The most debilitating side effect observed was cytokine release syndrome (CRS) that is characterized by the release of various inflammatory cytokines like C-reactive protein (CRP), ferritin, interferon (INF)-ϒ, and various interleukin (IL-1, IL-2, IL-4, IL-6 and TNF).[6] The first presentation of CRS as observed in various literature is fever with variable pattern and developing at different days following the infusion of CAR T-cell therapy.

Some studies have even shown the development of fever on the very next day of therapy followed by day 9 and day 14 of the therapy.[7] The other symptoms associated with CRS are hypotension, hypoxia and sinus tachycardia as well.[7] The CRS is not only a single disease entity, actually it is a set of disorders

that can be vary from just fever to hypotension requiring vasopressin and finally cardiac and respiratory depression leading to death. The most commonly used management options are immediate use of corticosteroids and tocilizumab (IL-6 receptor inhibitor) as well as supportive care.[8]

The second most common toxicity associated with CAR T cell therapy is immune effector cells mediated neurotoxicity that is manifested as delirium, hallucinations, seizers, dysphagia, nerve palsies and motor and sensory defects due to white matter degeneration of brain tissue.[9] The neurological symptoms were also presented as encephalopathy secondary to hepatic failure leading to CAR T cell mediated encephalopathy. The neurotoxicity urgently warrants the use of corticosteroids (high dose dexamethasone) for prevention of long-term neurological consequences.[10] Similar to the variability in the development of fever, the neurological manifestation was also showing variability in the disease course, being developing from the day following the three to four weeks that need vigilant attention in this regard.[11] Though the toxicities associated with CAR T-cell therapy are debilitating, but the benefits we getting and the revolutionary pillar the therapy has been built is outrageous. So, there is dire need of getting innovation in this field as well because the toxicities associated with CAR T-cell therapy are really the point of concern in this era of paramount excellence in the field of oncology and hematology.

These toxicities related limitations have served as a strong incentive to develop strategies to ensure safety, and another potential avenue to ameliorate CAR-T cell toxicity is through implementing of various strategies like CAR off switches, suicide gene strategies, modifying the CAR transduced T cells, and altering the affinity of the CAR-T cell's antigen binding domain. Thus, preventing the toxicities and maintaining the effectiveness of CAR T-cell therapy in fighting against various malignancies along with perspective role in solid tumors as well.

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