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Adverse Events and Side Effects of Chimeric Antigen Receptor (CAR) T Cell Therapy in Patients with Hematologic Malignancies

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Abstract

Chimeric antigen receptor (CAR) T cell therapy is rapidly being established as a new cancer treatment modality especially for the treatment of hematologic malignancies. Alongside being capable of inducing durable responses in such malignancies, CAR T cell therapy has always been accompanied by exclusive toxicities such as cytokine release syndrome (CRS), that can range from mild to life-threatening. These toxicities require intensive monitoring and fast and executive management procedures to reduce the level of damages or the rate of mortality in CAR T cell therapy recipients. In this review, we tend to introduced some of the most common CAR T cell therapy-related toxicities and their clinical demonstrations. Furthermore, we also introduce some of the management procedures commonly considered in this regard.

Keywords: Chimeric Antigen Receptor, Cancer Immunotherapy, Toxicities, Clinical Management, Cytokine Release Syndrome

1. Context

Cellular immunotherapy using T cells genetically modified to express chimeric antigen receptors (CAR T cells) has been efficacious in selectively redirecting the cytotoxicity of T lymphocytes towards tumor cells of interest (1). To this date, this type of therapy has been investigated in a wide spectrum of malignancies from hematologic malignancies to solid tumors (1-6). CAR molecules are the result of combining synthetic biology with basic immunology and cancer science (7, 8). They are made of an extracellular domain (responsible for the redirection and binding of CAR T cells to the target antigen expressed on the surface of cancer cells), a hinge, a transmembrane domain, and an intracellular domain (consisted of one or two co-stimulatory domains and an activation domain) (7, 9-11). The extracellular domain is the antigen-recognizing targeting domain of CARs which are usually based on the single-chain variable fragment (scFv) of a monoclonal antibody (7, 11-13). Variable single domains of camelid heavy-chain-only antibodies (known as VHH or nanobodies®) have also been known as potent targeting domains for the construction of CAR molecules (1, 14-20). Moreover, together, the costimulatory domain (s) (such as CD28, OX40, and 4-1BB) and the activation domain (derived from the CD3ζ of T cell receptor) of CARs are responsible for the activation of the engineered T cell upon target antigen engagement (7, 21). The co-stimulatory domain of CARs severs as a helping hand to the activation domain in the process of CAR T cell activation upon target antigen engagement (21). CAR T cells harboring co-stimulatory domains (such as the second-generation and the third-generation CAR T cells, which have one and two costimulatory domains, respectively) have exhibited superior tumoricidal activity in the clinics, as compare with CAR T cells having only an activation domain (known as the first-generation CAR T cells) (8, 22, 23).

CAR T cell therapy has demonstrated its ability in mediating promising results in various hematologic malignancies (1, 11, 24-26). The clinical approval of CAR T cells by the US Food and Drug Administration (FDA) began with Tisagenlecleucel for the treatment of patients with relapsed and/or refractory (R/R) B-cell acute lymphoblastic leukemia (B-ALL) (4, 27, 28). Later, the sequential FDA approvals of CAR T cell products continued with axicabtagene ciloleucel for diffuse large B-cell lymphoma (DLBCL), brexucabtagene autoleucel for mantle cell lymphoma (MCL), and lisocabtagene maraleucel for DLBCL (1, 29-32).

With becoming more popular and as investigated more in clinics, CAR T cell therapy-related toxicities were identified with more detail (1, 10, 13). CAR T cell-

related toxicities such as cytokine release syndrome (CRS), macrophage activation syndrome (MAS), neurological toxicities, tumor lysis syndrome (TLS), etc. are different from the toxicities of the traditional cancer treatment methods (33-36). In some cases, patients suffering from these toxicities require meticulous clinical attention (33, 34). Therefore, to get to know such toxicities and how they manifest themselves in detail can give us a better overview of how we can find efficient strategies to prevent, mitigate, or manage them (37-39). In this review, we try to introduce some of the most common CAR T cell therapy-related toxicities. Furthermore, we briefly discuss how these toxicities manifest themselves.

2. Examples of Favorable Clinical Outcomes

CAR T cells targeting CD19 have shown promising and encouraging results in the treatment of certain lymphomas and leukemia and have proven themselves as trustable novel anti-cancer therapeutics throughout different courses of clinical investigations (1, 40-42). Completed clinical trials which have released their results regarding the utilization of genetically modified T cells equipped with a chimeric receptor for the treatment of ALL have shown encouraging clinical outcomes. Such outcomes include leukemia-free states as declared by high-resolution flow cytometry in 27 out of 29 patients (93%) (43) and complete remission (CR) sustained for up to 2 years in 27 out of 30 patients (90%), 15 of whom had already undergone stem-cell transplantation and 2 others with the blinatumomab-refractory disease (44).

In 2016, Brudno et al. reported minimal residual disease (MRD)-negative CR in 4 out of 5 patients (80%) (45) while Lee and colleagues reported CR in 14 out of 20 patients (70%) and MRD-negative CR in 12 of these patients (60%) with an estimated leukemia-free survival rate of 78.8% and 51.6% at a median follow-up of 4.8 and 10 months, respectively (46). In 2013, Grupp et al. reported morphologic remission with an MRD of $< 0.01\%$, approximately 1 month after the therapy in two children which was only refractory in one due to the presence of CD19-negative blasts (47). The abovementioned clinical results can be viewed as a clinical victory and lead us to the conclusion that genetically modified T-cells, equipped with a chimeric receptor for anti-cancer therapy, are close to being recognized as a universal platform for the treatment of various types of hematologic malignancies.

Since two patients, who were central nervous system (CNS) leukemia-positive at the time of enrollment, achieved remission as the level of CAR T cells elevated in their cerebrospinal fluid (CSF) (46), it is safe to hypothesize that the migration of CAR T cells into the CFS can be viewed as a highly efficient mechanism for the prevention of possible relapse in the CNS (48). Furthermore, this phenomenon might also suggest that CAR T cell therapy might be an ideal future choice for the treatment of primary CNS cancers and CNS lymphomas (47). CAR T cell therapies, despite their favorable clinical outcomes, are also intertwined with various unwanted side effects which might limit success rate or their broader application. In the next section, we will briefly discuss those adverse events and highlight the clinical interventions used for their management and resolution, so far.

3. Toxicities and Management

3.1. CRS

CRS as the name implies is characterized by pronounced multi-cytokine over-flood resulting from an immune system hyperactivation caused by rapid T-cell stimulation and proliferation (1). CRS has been a common toxicity engaged in almost every clinical trial investigating anti-CD19 CAR T cells as a suitable therapy for hematologic malignancies. Fever (44-47, 49-51), tachycardia (45, 50, 51), hypotension (44-47, 50, 51), acute respiratory distress syndrome (47, 51), and multiorgan failures are examples of which CRS manifests itself as and they can range from mild to a series of life-threatening complications (44-47, 49-51). It is important to keep in mind that patients with CRS-related life-threatening toxicities might require meticulous intensive medical care based on the severity level of this adverse event.

Clinical investigators have reported many CRS-related profiles of cytokine levels such as elevated levels of soluble interleukin (IL)-1 receptor α, IL-2, IL-2 receptor (47) soluble IL-2 receptor (44), IL-6 (43, 45-47), IL-10 (43, 46, 47), interferon γ (43, 44, 46, 47), GM-CSF (43, 46), TNF-α (47), and lactate dehydrogenase (LDH) (45, 47, 51). The multi-cytokine profile patterns of CRS mirror those of the MAS and they have similarities in terms of laboratory findings and clinical manifestations (47, 49, 51-55). Anti-cytokine therapy, consisting of tocilizumab, a humanized monoclonal antibody against the IL-6 receptor, has been suggested and clinically applied as the first-line agent for the resolution of CRS (44, 46, 47, 51, 56, 57), due to its rapid response and effectiveness in the reversal of the syndrome without any further negative impact on the antileukemic activity or expansion of CAR T cells (47). Moreover, it has been reported that corticosteroids, occasionally used for CRS and CRS-related toxicity resolution alongside tocilizumab, despite their slight positive effects, have profound negative effects on CAR T cell persistence and proliferation while administered in high doses for the management of CRS (47,

50, 56-58). There also lies a strong correlation between CRS severity and the patient's disease burden, with higher disease burden resulting in more severe CRS clinical and laboratory manifestations (46).

3.2. Severe CRS

Laboratory features attributed to severe CRS (sCRS), not an uncommon toxicity caused by CAR T cell therapy of cancers (43, 44, 46, 47), includes higher peak levels of IL-6, interferon γ (44, 46), ferritin, soluble IL-2 receptor (44), which were higher than those in patients with CRS, as well as elevated prothrombin and coagulopathy (44). Bleeding, vasopressor-requiring hypotension, and ICU-requiring respiratory failure are also among other clinical manifestations caused by sCRS (44).

A pronounced correlation exists between the probability of sCRS development and the degree of disease burden, in a way that higher disease burden increases the risk of sCRS development (43, 44). Besides the fact that the commercially approved monoclonal antibody tocilizumab is considered for the treatment of sCRS (44), collectively, two sCRS- and multiorgan failure-induced mortalities have been documented (with one of them being uncreative to tocilizumab, etanercept, and corticosteroids) (43).

3.3. MAS

MAS is a serious life-threatening complication resulting from the hyper-activation and excessive proliferation of macrophages and T lymphocytes (59). MAS-related clinical manifestations following the administration of CAR T cells include hyperinflammation (49), fever (49, 51), and hepatosplenomegaly (47, 49, 51), alongside laboratory features such as cytopenia, elevated soluble IL-2 receptor α levels, hyperbilirubinemia (49, 51), elevated levels of aminotransferases (47, 49), LDH (47, 51), and coagulopathy (47, 51), as well as abnormally elevated cytokine profiles (47).

3.4. Tumor Lysis Syndrome (TLS)

Tumor lysis syndrome (TLS) refers to the constellation of metabolic contents released into the bloodstream as a result of tumor cell lysis caused by anti-cancer therapies. Such metabolic contents can eventually cause medical conditions such as hyperphosphatemia, hyperuricemia, and hyperkalemia (60). Since TLS is a result of cellular death byproducts, the larger the tumor burden or the faster the tumor cell proliferation speed is, the more likely and frequent it is for TLS to occur (61). Moreover, TLS has also been frequently associated with elevated levels of LDH occasionally accompanied by fever (47).

3.5. Graft-Versus-Host Disease

Graft-versus-host-disease (GVHD) is an immune response that can have adverse effects on the CAR T cell recipient's vital organs and it may require the administration of immunosuppressive drugs (which in their way increase the risks of infectious diseases and other immunosuppression-related complications) (62). Since the early days of considering this therapy for the treatment of ALL, GVHD has not been a famous complication in post-transplant patients (43-47, 63). However, only one case of chronic GVHD development in a patient with previous acute skin GVHD has been reported which had happened 3 months after the beginning of the therapy (43). Subsequently, treatment with corticosteroid was considered suitable for the management of the incidence in this case (43).

3.6. Constitutional CRS

Constitutional CRS-related occurrences, which are more general and cannot be meticulously categorized, also manifest during the onset of the cytokine syndrome. The first and most common of these occurrences is fever (44-47, 49-51), which surfaces earlier than any other general clinical manifestations of CRS as well as multiple subsets of fatigue (50).

3.7. Hepatic Complications

Liver-related laboratory findings such as hyperbilirubinemia (45, 49, 51), elevated levels of aspartate aminotransferase (AST) (45, 47), alanine aminotransferase (ALT) (45, 47, 51), and alkaline phosphatase (ALP) (45) have all been reported in numerous CAR T cell clinical trials. Collectively, these complications led to the conclusion of naming hepatic dysfunction as the most common type of organ dysfunction following the administration of CAR T cells (51).

3.8. Pancreatic Complications

Toxicities that affect the pancreas are not deemed popular and are much less reported with pancreatitis development only being reported in 5 patients (approximately 13%) following the commencement of CAR T cell therapy (51).

3.9. Renal Complications

Acute kidney injury (AKI) refers to a clinical syndrome characterized by the accumulation of nitrogen metabolism products, such as urea, and a subsequent decline in renal excretory rate alongside a decrease in urine output commonly caused by sepsis (64). This complication has rarely been engaged in the adverse events caused by genetically manipulated T cells and has been known to range

from mild to stage 2 or 3 of the syndrome (51) alongside other kidney-related toxicities categorized as renal electrolyte imbalances (45, 46).

3.10. Pulmonary Complications

The respiratory system can also be affected by the toxicities caused by this treatment modality. Pulmonary complications include hypoxia (45, 46, 50), dyspnea (45), intensive care unit requiring CRS-related respiratory insufficiencies (44), acute respiratory failure (which could be resolved with the help of invasive mechanical ventilation), and acute respiratory distress syndrome (ARDS) (51). Of note, it has been reported that grade 4 ARDS can be treated with a single course of etanercept and tocilizumab without the need for further vasoactive medications or ventilator support (47).

3.11. Cardiovascular Complications

Adverse events having substantial impacts on the cardiovascular system have appeared commonly and included tachycardia (45, 50, 51), hypotension (44-47, 50, 51), hypertension, cardiac arrest (46), vasoplegic shock (51), and systolic dysfunction (45, 46, 51).

3.12. Musculoskeletal Complications

Myositis characterized by muscle inflammation (45), along with elevated levels of creatine phosphokinase (CPK) (occasionally associated with both muscle pain and weakness) (45, 46), and CRS-related myalgias (51) are collectively among the most common clinically unfavorable adverse events influencing the muscular system following CAR T cell therapy.

3.13. Gastrointestinal Complications

Gastrointestinal complications were also experienced by the respective patients which included diarrhea (45, 50), nausea (45), mild mucositis (43) (which refers to the inflammation of the digestive tract lining mucous membranes), as well as colitis possibly originated from an infectious cause (45).

3.14. Hematologic Complications

Various hematologic complications have been reported in clinical trials of CAR T cell which include thrombocytopenia (45, 46, 51), anemia, (45, 46), neutropenia (45, 46, 50), febrile neutropenia (43, 45-47, 50), lymphocytopenia, and leukopenia caused by lympho-depleting chemotherapy (46). Furthermore, hypofibrinogenemia (47, 49, 51), intravascular coagulation (43), and B-cell aplasia (occasionally in a prolonged fashion) (44, 47) have all been found to be some other hematological adverse events documented by the relative clinical investigations.

3.15. Neurologic Toxicities

Toxicities impacting the nervous system have played a lead part from the conception of this type of cell therapy. In detail, higher levels of IL-6, IFN-γ, and TNF-α, at the beginning of the therapy could subsequently act to increase the likelihood of grade 3 or higher severe neurotoxicity development (43, 44). Moreover, IL-6 concentration itself is a factor of paramount importance for the development of grade 3 or higher neurotoxicity according to univariate logistic analysis (43). However, since there have been cases in which the neurologic toxic effects were unpreventable by anti-cytokine therapy consisting of tocilizumab, it might be considerate to conclude that there is no correlation between the severity of CRS and the occurrence of neurotoxicity (44). The correlation between the development of neurotoxicity and the administration of genetically manipulated T-cells is due to their migration into the CSF of the respective patients which, with a look on the bright side, can also play a powerful role in the elimination of CSF leukemia (46, 47).

Other common neurologic side effects of CAR T cell therapy may include headaches (45, 46), confusion (44, 51), tremor (46), hallucinations (44, 46, 51), encephalopathy, (43, 44, 47, 51), and seizures (43, 44, 46, 50, 51). Except for one reported fatality due to severe irreversible neurologic deficits (122 days after the beginning of the therapy), the complete disappearance of the neurologic toxicity manifestations over days to weeks is noteworthy (43).

3.16. Infectious Diseases

Patients with leukemia who are enrolled in CAR T cell therapy clinical investigations usually undergo lympho-depleting chemotherapy prior to the administration of the CAR T cells (1). This procedure leads to the debilitation of the recipients' immune system which makes them inviting and welcoming hosts for adverse effects caused by opportunistic infections (1). In detail, colitis development (possibly caused by a previous infection which had eluded the weakened immune system) (45), urinary tract infection (50), and other likely opportunistic infections can be mentioned as examples in this regard (51).

4. Conclusions

The undisputable benefit of CAR T cell therapy has been demonstrated in various hematologic malignancies unresponsive to the commonly available treatment methods. However, comprehensive knowledge for the management and prevention of the early and late adverse events of this type of therapy is an extremely crucial factor for creating successful clinical outcomes. So far, many strategies have

been proposed for the prevention and mitigation of some of the herein discussed toxicities (which are comprehensively discussed elsewhere) (10, 13, 65-67). However, there are remaining ambiguities regarding the prevention or management of several of these adverse events. As our knowledge of the detailed mechanism of action and the clinical demonstration of these toxicities evolves, it will be much easier to predict their onset once the early signs emerge. Therefore, it will also be easier to manage the unwanted damages and to unleash the tumoricidal power of this type of anticancer therapy.

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