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Challenges and innovations in managing cytokine release syndrome in CAR-T therapy: mechanisms, clinical impact, and future directions

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Abstract. Chimeric Antigen Receptor (CAR) T-cell treatment represents a groundbreaking advancement in cancer immunotherapy, particularly for blood-related cancers. Nevertheless, its therapeutic application is sometimes hindered by Cytokine Release Syndrome (CRS), an inflammatory response that has the potential to be life-threatening. This review explores the underlying causes of CRS, its clinical symptoms, and the difficulties encountered in treating affected people. In addition, we investigate contemporary treatment methods, such as administering tocilizumab and utilizing kinase inhibitors and CAR-NK cells, to mitigate the severity of CRS while maintaining the effectiveness of CAR-T cell therapy. In addition, we emphasize upcoming advancements in CAR-T technology, including reversible and irreversible CAR switches, which are intended to improve both safety and therapeutic results. This study emphasizes the continuous requirement for research to enhance CAR-T cell treatment by finding a middle ground between optimizing its effectiveness and guaranteeing patient safety.

Keywords: Cancer, Immunotherapy, CAR-T cell therapy, Cytokine release syndrome, CAR-NK cell.

1. Introduction

Cancer immunotherapy has revolutionized how we treat cancer by utilizing the ability of the immune system to identify and eliminate cancer cells. This approach provides a compelling alternative to traditional treatments [1]. Among the several immunotherapy methods, Chimeric Antigen Receptor (CAR) T-cells are notable for their novel design, which allows them to target and kill tumour cells precisely. CAR-T cells are genetically engineered to produce receptor proteins that will enable them to identify antigens found in cancer cells. This combines the cancer-killing abilities of T cells with the precise targeting and binding solid properties of monoclonal antibodies (mAbs). Unlike tumour-infiltrating lymphocytes (TILs), CAR-T cells can recognize antigens independently of the major histocompatibility complex (MHC), avoiding cancer cells' typical immune evasion strategies [2–4].

The notion of a chimeric T-cell receptor was initially proposed in 1987. By 1989, substantial progress had been made to enable T cells to identify antigens regardless of the MHC [5, 6]. Over time, CAR-T cell therapy has advanced to its fourth generation, which enhances the effectiveness of previous generations by triggering cytokines and chemokines production upon recognizing antigens. This leads to the continuous activation of CAR-T cells and the recruitment of natural immune cells to overcome

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the immunosuppressive tumour microenvironment (TME) [3, 7]. Since its initial FDA clearance in 2017, CAR-T cell therapy has shown significant potential, especially in treating hematological cancers [8].

Although CAR-T cell treatment can bring about significant changes, it also poses considerable difficulties due to the toxicities it relates to [9]. A substantial percentage of patients, particularly those undergoing treatment for acute lymphoblastic leukemia or lymphoma, encounter different degrees of toxicity, with adverse severe responses documented in 23-46% of instances [10]. These severe toxicities often occur due to an excessive release of cytokines and the rapid growth of T-cells, leading to a potentially life-threatening condition called Cytokine Release Syndrome (CRS) [11]. CRS is a pathological state marked by systemic inflammation resulting from CAR-T cell activation and proliferation. Consequently, there is an elevation in inflammatory cytokines production, leading to fever, muscle soreness, fatigue and other symptoms. [10, 12].

This study seeks to thoroughly examine CRS within the framework of CAR-T cell therapy, with a specific focus on its frequency, underlying mechanisms, and the therapeutic difficulties it presents. Furthermore, the study explores the molecular underpinnings underlying CRS and explores novel strategies to mitigate its impact while maintaining the effectiveness of CAR-T cell therapy.

2. Understanding CRS

2.1. Pathophysiology of CRS

The cytokine profile associated with CRS arises from the activation of multiple immune cell types. Interleukin-6 (IL-6), generated mainly by activated macrophages and monocytes, plays a critical role in increasing CRS, with higher levels of IL-6 linked to increased severity [13, 14]. Interleukin-1 (IL-1) additionally induces the production of IL-6 and activates nitric oxide synthase. High levels of supplementary cytokines are commonly spotted in the circulatory system and are generated by CAR-T cells, other activated T cells, or myeloid cells. Severe CRS is typically identified by elevated levels of granulocyte-macrophage colony-stimulating factor (GM-CSF), while activated CAR-T cells increase the expression of GM-CSF receptors [15]. In severe cases, the cytokine patterns closely match those seen in macrophage activation syndrome/hemophagocytic lymphohistiocytosis (MAS/HLH). The observed capillary leakage in CRS could be exacerbated by endothelial activation, characterized by elevated von Willebrand factor and angiopoietin-2, as well as decreased angiopoietin-1 [13, 14].

The development of CRS with CAR-T treatment progresses through well-defined stages. Initially, CAR-T cells migrate to the tumour site, recognizing and targeting cells that display the specific antigen. This recognition triggers CAR-T cell proliferation, cytokines production, and the stimulation of innate immune cells, leading to the onset of CRS. Elevated cytokine concentrations and CAR-T cell proliferation in the circulatory system initiate a pervasive inflammatory reaction, impairing endothelial cells, vascular permeability, and organ injury. In the final phase, the demise of T cells resulting from activation triggers a decline in levels of cytokines and inflammation, finally resolving the symptoms of CRS once the tumour has been eradicated [16].

2.2. Clinical presentation of CRS

Most instances of CRS usually occur within 14 days after the infusion of CAR-T cells and typically persist for 7 to 8 days [15]. Fever is invariably the first symptom, often exceeding 105°F (40.5°C). The initial indication of the illness is a high fever, frequently over 105°F (40.5°C), accompanied by influenza-like symptoms such as muscle soreness, headaches, chills, general discomfort, and reduced desire to eat. Although most CRS episodes cure spontaneously, severe instances have the potential to progress and mimic diseases such as sepsis or capillary leak syndrome. These severe symptoms may include low blood pressure, rapid heart rate, fluid buildup in the lungs, swelling, and low oxygen levels. These symptoms can fail multiple organs, often requiring critical care [12, 17, 18]. Severe CRS can lead to hypofibrinogenemia and disseminated intravascular coagulation (DIC). Patients may show increased troponin levels and decreased ejection fraction [15]. C-reactive protein (CRP), ferritin, and other indicators of widespread inflammation are often seen at high levels in severe CRS [13, 19].

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The CRS grading systems provide an impartial method for assessing the seriousness of CRS by considering clinical indications and symptoms. This aids in making informed choices regarding anti-cytokine therapies. The National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 has been employed to characterize CRS outcomes in patients who received blinatumomab and other therapeutic antibodies. Nevertheless, this system was created for conventional medications, considering the seriousness of symptoms and the choice to temporarily halt drug infusions or intervene, which may not be entirely relevant to cellular therapies such as CAR-T. It is worth noting that a patient's CRS grade may vary depending on the grading system used [12]. Therefore, specialized grading systems have been created to account for the unique characteristics of CAR-T-induced CRS [20]. The American Society of Transplant and Cellular Therapy (ASTCT) has implemented a standardized grading system, which is expected to be more widely utilized in upcoming CAR-T trials. This approach classifies CRS according to the presence of a fever and evaluates its severity by considering factors such as the requirement for supplemental oxygen and vasopressors [21].

2.3. Risk factors for CRS

Clinical research has discovered various indications that can accurately predict the severity of CRS. The likelihood of developing CRS is impacted by aspects related to the treatment modality, the patient's underlying medical condition, and individual patient characteristics. The intensity of CRS after CAR T-cell therapy has been associated with various clinical factors. The patient's disease burden significantly impacts the intensity of CRS following CAR T-cell therapy. In a murine lymphoma model, mice with a substantial tumour burden, after CAR-T cell therapy, experienced fatal. In contrast, individuals with smaller tumours exhibited no signs of CRS. The dosage delivery of the therapeutic medication also affects the risk of CRS. Moreover, the extent of T-cell activation and the magnitude of T-cell proliferation are strongly linked to the intensity of CRS. Children are more susceptible to contracting CRS than adults [22].

3. Challenges posed by CRS

3.1. Impact on patient safety and outcomes

Patients with CRS can experience a wide range of organ dysfunctions as the syndrome progresses. Myalgia, often linked to elevated creatine phosphokinase levels, suggests the presence of inflammatory muscle damage. Additionally, there could be transient elevations in bilirubin and liver enzymes, suggesting potential hepatitis and liver dysfunction [23, 24]. Renal impairment, marked by a temporary increase in serum creatinine levels, may also occur [14]. Cardiovascular complications are common after CAR-T cell therapies in both adults and children, potentially leading to heart failure. CRS can further aggravate these cardiovascular issues, increasing the risk of adverse outcomes [24].

Out of the 262 patients that were part of the trial, 74.4% of them had CRS. However, the study found no significant difference in the length of time patients lived without disease progression or their overall survival rates between those with CRS and those without. This finding is consistent even when comparing patients with moderate CRS and those with more severe CRS. Furthermore, the researchers observed no significant difference in response rates between patients who experienced CRS and those who did not [25]. These results suggest that while CRS can cause severe complications, its presence does not necessarily impact long-term patient outcomes.

3.2. Challenges in clinical management

Clinically managing CRS poses significant challenges due to its nonspecific symptoms, making accurate diagnosis difficult. It is essential to differentiate CRS from other inflammatory conditions with similar clinical presentations, as these conditions may require distinct treatment strategies [22].

One such condition is tumour lysis syndrome (TLS), which resembles CRS. Although TLS can typically be distinguished from CRS by its characteristic laboratory abnormalities, there are cases where differentiating between the two is complex, mainly if both conditions co-occur [26].

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Differentiating CRS from sepsis is equally important, as treating sepsis with therapies suited for CRS can be harmful. However, this distinction is often challenging. According to current definitions, numerous patients with severe CRS might meet the clinical standards for sepsis [27]. This overlap underscores the importance of accurate diagnosis to ensure appropriate and effective treatment.

4. Current strategies to mitigate CRS

4.1. Therapeutic interventions

Supportive care is typically adequate for managing low-grade CRS. However, severe CRS, characterized by fluid-refractory hypotension or respiratory failure, requires more aggressive treatment. In such cases, anti-IL-6 therapy, particularly with tocilizumab, is preferred over corticosteroids [17]. Although corticosteroids are effective, they can weaken CAR-T cell function and must be reserved for life-threatening situations where IL-6 therapy is insufficient [28].

Tocilizumab, an IL-6 receptor inhibitor, has proven potent for CRS management without diminishing the CAR-T cell efficacy or inducing significant side effects [28]. The FDA has approved tocilizumab for treating CAR-T-associated CRS for patients who are two years old and older. Based on its use in rheumatologic diseases, the primary side effect of tocilizumab is an increased risk of bacterial infections. However, it does not appear to impair the short-term humoral response to pneumococcal vaccination. Studies have shown that tocilizumab does not lead to adverse outcomes when used to treat CAR-T-associated CRS and is associated with rapid clinical improvement in severe cases [29]. Additionally, tocilizumab has effectively treated severe CRS induced by other therapies, such as PD-1 inhibitors and post-haploidentical stem cell transplants [28, 30].

4.2. Modifying CAR-T therapy to reduce CRS

Novel strategies are being investigated to decrease the frequency and severity of CRS by changing CAR-T therapy. The technique exploits kinase inhibitors' restricted selectivity to create a controllable on/off mechanism for CD3ζ chain-based CAR-T cells. For instance, dasatinib, a kinase inhibitor specifically targeting BCR-ABL, has effectively and temporarily suppressed the harmful effects of CAR-T cells and cytokines secretion. Dasatinib, when given to preclinical mice for a short time, reduced the death rate caused by CRS without affecting the effectiveness of CAR-T cells. The medication cessation restored the standard functionality of CAR-T cells [31].

Another approach centers around diminishing LCK signalling by manipulating the enlistment of the phosphatase SHP. By reducing the generation of effector cytokines by CAR-T cells, the severity of CRS is lessened [32]. In preclinical investigations, changes to the BBz CAR have shown promising results. These modifications have mitigated CAR-T cell activation and decreased cytokines production, thereby successfully reducing toxicity [33].

5. Future directions in addressing CRS

5.1. CAR-T cell switches

The development of reversible switches in CAR-T cell therapy represents a significant advancement, offering the ability to temporarily control CAR-T cell activity through chemically disruptable mechanisms [34]. One approach employs a STOP CAR design involving two functional chains: the recognition (R) chain and the signalling (S) chain. These chains are dimerized using a protein pair (apoE4 and Bcl-XL) [35]. Disruption of this dimerization by a specific inhibitor can transiently inactivate CAR-T cells. Another promising method utilizes proteolysis-targeting chimera (PROTAC) technology, wherein adding a small molecule such as lenalidomide induces the degradation of the CAR molecule. A third strategy involves using SWIFF-CARs, which incorporate cleavable degrons regulated by the HCV NS3 protease, allowing for controlled CAR degradation [36]. However, while these reversible switches provide temporary control, they require additional genes, which is challenging given the limited viral payload capacity. An alternative design employs a camelid antibody that targets both

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the tumour-associated antigen (TAA) and methotrexate (MTX). MTX induces a conformational change that disrupts TAA binding, thereby inactivating CAR-T cells [37].

Irreversible switches provide a lasting resolution to halt the CAR-T cell activity, which is especially beneficial in managing severe cytokine-mediated toxicities. One strategy utilizes complement-dependent cytotoxicity (CDC) and antibody-dependent cell-mediated cytotoxicity (ADCC). Therapeutic antibodies target and neutralize CAR-T cells created with specific surface antigens in this approach. While this strategy is effective, it may require increased speed. The inducible caspase 9 (iCasp9) system is an expedited option, which induces programmed cell death in CAR-T cells when stimulated by rimiducid. This method has been proven in clinical settings, effectively decreasing severe symptoms within a few hours. Additional irreversible techniques encompass the employment of the HSV-tk/ganciclovir system, which triggers the demise of CAR-T cells. However, this strategy is constrained by its comparatively delayed efficacy and the possibility of provoking an immune response [34]. Moreover, temporary CAR expression can be accomplished by introducing mRNA through transfection, resulting in a CAR-T cell product that is "biodegradable" and reduces the potential for sustained excessive activation. However, this approach requires several infusions [38].

5.2. CAR-NK cells

CAR-NK cells provide a promising alternative to CAR-T cells, delivering enhanced safety in different therapeutic situations. Unlike CAR-T cells, original Natural Killer (NK) and CAR-NK cells have reduced longevity, decreasing the probability of on-target/off-tumor toxicity [39]. One significant benefit of CAR-NK therapy is its decreased probability of causing CRS and neurotoxicity, ascribed to activated NK cells' unique cytokine profile, such as Interferon-gamma (IFN-γ) and GM-CSF. Conversely, CAR-T cells trigger a more extensive release of cytokines, many closely linked to CRS [40].

6. Conclusion

CRS is a significant constraint in the practical use of CAR-T cell treatment since it can induce severe and perhaps fatal adverse reactions. Although CAR-T cells demonstrate considerable potential in treating blood malignancies, the toxicities that come with it, especially CRS, require careful assessment and creative approaches to control. Comprehensive knowledge of the pathophysiology of CRS, which encompasses its cytokine-mediated processes and many clinical presentations, is essential for developing efficacious treatments.

Present techniques, such as the use of tocilizumab and alterations in CAR-T cell composition, have shown usefulness in reducing CRS while preserving the efficacy of CAR-T cells. Furthermore, the exploration of innovative methods such as reversible and irreversible CAR-T switches, along with the advancement of CAR-NK cells, shows potential for improving the safety and effectiveness of immunotherapy.

As research advances, it will be essential to incorporate these groundbreaking approaches to improve CAR-T cell treatment, thereby maximizing its life-saving capabilities and minimizing potential risks to patient safety. In the future, it will be crucial to adopt a multidisciplinary approach that combines clinical knowledge with advanced research to effectively address CRS issues and fully realize CAR-T cell treatment's potential.

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