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A Review

ADVERSE EVENTS AND SAFETY PROFILE OF CAR T-CELL THERAPY – A COMPREHENSIVE REVIEW

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A B S T R A C T

Chimeric Antigen Receptor (CAR) T-cell therapy has emerged as a ground breaking immunotherapy for various haematological malignancies and solid tumors. While CAR T-cell therapy has shown remarkable efficacy, it is also associated with unique safety concerns and toxicities. This comprehensive review article aims to provide an in-depth analysis of the safety profile and toxicity considerations in CAR T-cell therapy. It will cover the mechanisms underlying CAR T-cell-related toxicities, such as cytokine release syndrome (CRS), neurotoxicity, on-target/off-tumor effects, and long-term complications also discuss risk stratification, prevention strategies, and the management of these toxicities, highlighting recent advances in toxicity management and mitigation approaches. Furthermore, it explores emerging technologies and interventions aimed at improving the safety profile of CAR T-cell therapy, including gene editing techniques, synthetic receptors, and engineered CAR T-cell platforms.

INTRODUCTION

CAR T-cell therapy, or chimeric antigen receptor T-cell therapy, was an innovative and personalized form of immunotherapy used to treat certain types of cancer which entails altering patient's own T cells, a type of white blood cell, to enhance their ability to recognize and destroy cancer cells [3.] It has shown remarkable success in the treatment of certain types of blood cancers, such as Acute Lymphoblastic Leukemia (ALL) and Diffuse Large B-cell Lymphoma (DLBCL), particularly in patients who have not responded to conventional treatments.[1] However, it is a complex and highly specialized therapy that carries some risks and side effects, including cytokine release syndrome (CRS) and neurologic toxicities. The development of CAR-T therapy represents a significant advancement in the field of cancer treatment, offering new hope for patients with previously untreatable or relapsed cancers[2]. The future outlook for CAR-T therapy is promising, with ongoing research and advancements aimed at improving its efficacy, expanding its applications as combination therapy to different types of cancer, and addressing its limitations in accessability and affordability.

Cytokine release syndrome (CRS) is most commonly associated with the use of chimeric antigen receptor (CAR) T-cell therapy[10,14]. It is characterized by the release of a large amount of cytokines, which are signaling molecules that regulate immune responses. In some cases, this immune response can become overactive and result in CRS. The pathophysiology behind CRS involves a cascade of events that can lead to systemic inflammation and organ dysfunction[10]. When immune cells, such as T cells, encounter a stimulus like CAR T-cell therapy or immunotherapy, they become activated and initiate an immune response. The activated T cells recognize and bind to their target cells, such as cancer cells or cells expressing a specific antigen. This interaction triggers the activation of T cells and the release of cytokines [9].

Cytokine release syndrome (CRS)

These are small proteins secreted by immune cells that act as signaling molecules, regulating the immune response. In CRS, the release of cytokines is dysregulated and excessive, leading to an overwhelming immune response. The key cytokines involved in CRS include interleukin-6 (IL-6), interferon-gamma (IFN-γ), tumor necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1) [9-11].The released cytokines contribute to the amplification and perpetuation of the immune response, leading to a positive feedback loop. They activate other immune cells, such as macrophages and natural killer cells, which further release cytokines and amplify the inflammatory response. This results in a systemic increase in pro-inflammatory cytokines, known as a cytokine storm. The cytokine storm can cause widespread inflammation, endothelial activation, and increased vascular permeability [9,15]. The increased permeability of blood vessels allows immune cells and cytokines to enter tissues and organs, leading to tissue damage and dysfunction. Multiple organs can be affected, including the lungs, liver, kidneys, and heart [11].
The severity of CRS can vary widely, ranging from mild flu-like symptoms to life-threatening organ dysfunction. Severe CRS can lead to Acute Respiratory Distress Syndrome (ARDS), coagulopathy, hypotension, multi-organ failure, and

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CAR T-cell Therapy" - Mechanism of Action

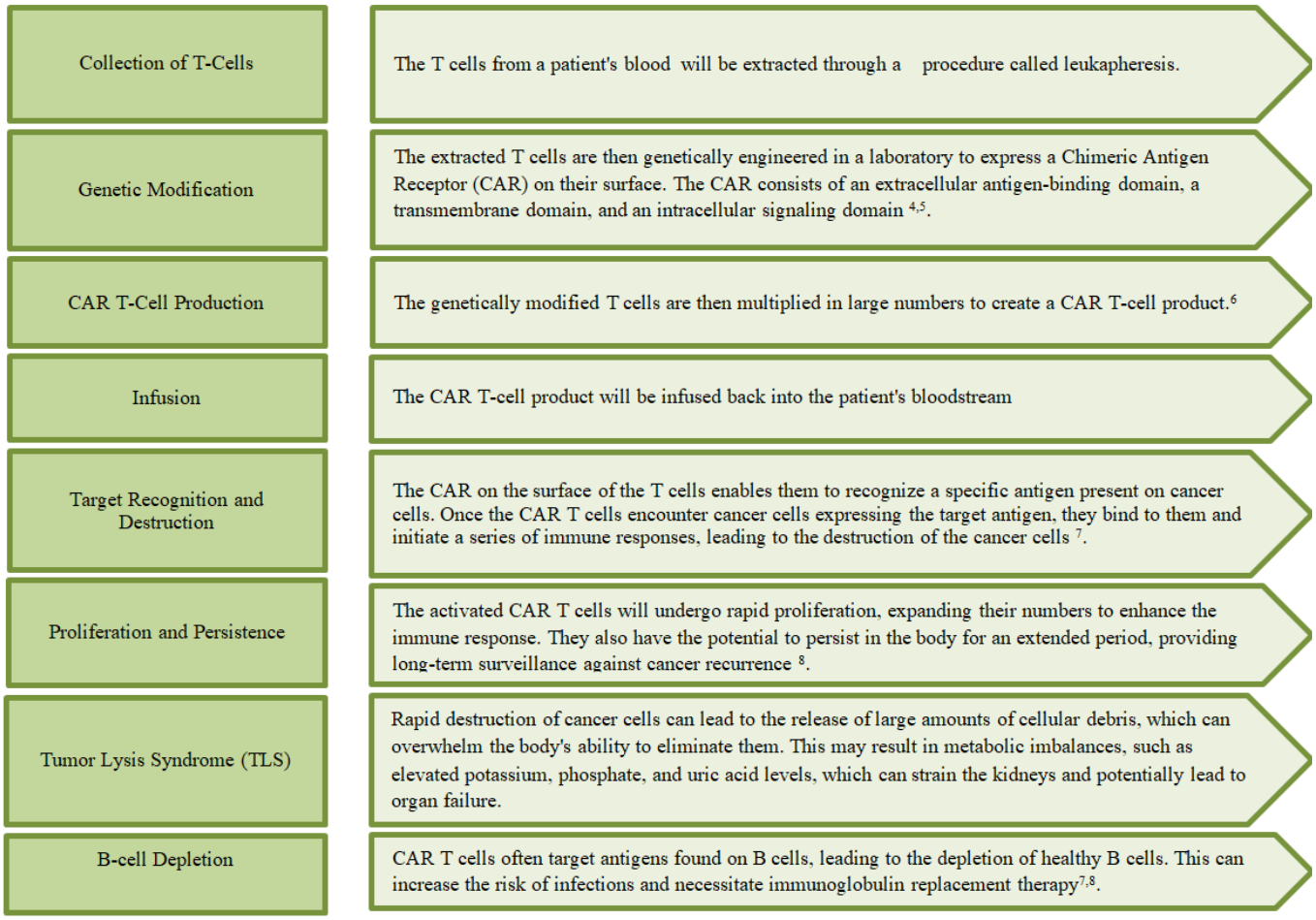

Fig. 1 CAR T-cell Therapy - Mechanism of Action

even death [12,13]. CRS management involves supportive care measures such as aggressive intravenous hydration, antipyretics, and supplemental oxygen can help manage CRS symptoms. In severe cases, intensive care unit (ICU) level care, including vasopressor support and mechanical ventilation, may be required [36].

Immune Effector Cell-Associated Neurotoxicity Syndrome (ICANS)

CAR T-cell-related neurotoxicity, also known as immune effector cell-associated neurotoxicity syndrome (ICANS), is a significant complication[16]. The incidence of CAR T-cell-related neurotoxicity varies depending on the specific CAR T-cell therapy and the targeted disease. It has been reported to occur in up to 50-70% of patients treated with CAR T-cell therapy [16]. It encompasses a wide spectrum of neurological manifestations like encephalopathy, motor symptoms, headache, aphasia and dysphasia, delirium. Certain risk factors associated for ICANS are disease burden, CAR T-cell characteristics, cytokine release Neurologic toxicities can range from mild confusion to life-threatening cerebral edema. Implementing strategies for close neurologic monitoring and early intervention, including neuroprotective medications and seizure prophylaxis, can help mitigate neurotoxicity [35]. ICANS can be approached by systemic corticosteroids, such as dexamethasone which help to mitigate the immune response and reduce inflammation.

Tocilizumab, an IL-6 receptor antagonist, can also be used in cases where neurotoxicity is associated with concomitant severe cytokine release syndrome and in refractory or severe cases, additional immunomodulatory agents, such as anti-IL-6 antibodies or other immunosuppressive therapies, may be considered [17].

On-target/off-tumor toxicities

Strategies to minimize toxicities associated with CAR T-cell therapy continue to be a focus of ongoing research and development [20]. By refining CAR designs, optimizing target selection, and implementing robust safety measures, the therapeutic window of CAR T-cell therapies can be improved which will maximize their efficacy and minimizing the risk of off-tumor toxicities [21].

Selection of target antigens: Choosing target antigens that are expressed predominantly or exclusively on cancer cells can help reduce the risk of targeting normal tissues. Extensive research and validation are crucial to identify antigens with minimal expression in healthy tissues. Development of safer CAR designs: Engineering CARs with optimized signaling domains and affinity can improve the specificity of CAR T cells. By carefully fine-tuning the CAR structure, researchers aim to enhance the discrimination between cancer cells and normal tissues, minimizing off-tumor toxicities[18]. Conditional control of CAR T-cell activity: Incorporating molecular

switches or suicide genes into CAR T cells allows for their conditional control [19].

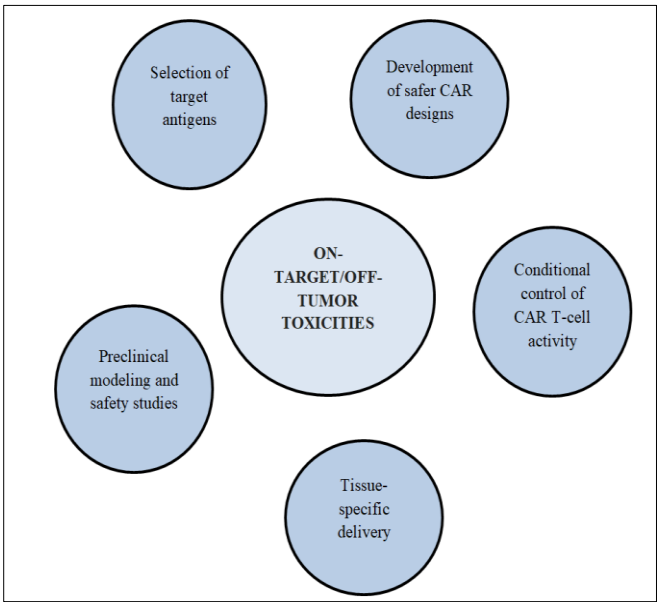

Fig. 2 Strategies to minimize toxicities associated with CAR T-cell therapy

These switches can activate or deactivate CAR T-cell activity, providing a means to modulate their function or eliminate them if toxicities arise. Tissue-specific delivery: Utilizing local delivery methods, such as intratumoral injection, can restrict CAR T-cell activity to the tumor site, reducing the exposure of normal tissues expressing the target antigen. Preclinical modeling and safety studies: Rigorous preclinical studies are essential to assess the potential toxicities of CAR T-cell therapy.[19] Animal models and advanced in vitro systems can help evaluate the safety and efficacy of CAR T cells and identify potential adverse effects in normal tissues.

Long-term complications

CAR T-cell therapy with its shown remarkable efficacy, it is important to consider the potential long-term effects associated with this therapy, including the development of secondary malignancies, organ toxicities, and autoimmune disorders. Although CAR T-cell therapy is designed to target cancer cells, there is a potential risk of developing secondary malignancies as a consequence of the therapy[27] . The prolonged persistence of CAR T cells and their potential to induce genetic modifications or insertional mutagenesis could contribute to the development of secondary cancers [27].CAR T-cell therapy can lead to organ toxicities, most commonly manifested as cytokine release syndrome (CRS) and neurotoxicity [28].This can also trigger autoimmune responses, leading to the development of autoimmune disorders. The activation and expansion of CAR T cells may result in unintended targeting of healthy tissues expressing the targeted antigen, leading to immune-mediated damage. These autoimmune responses can manifest as organ-specific or systemic autoimmune disorders, such as thyroiditis, hepatitis, or pneumonitis [29]. The occurrence of these long-term effects may vary depending on the specific CAR T-cell therapy, patient characteristics, and other factors. Regular monitoring, long-term follow-up, and further research are needed to fully understand and mitigate the long-term effects of CAR T-cell therapy

Risk stratification and predictive biomarkers

Evaluation of risk factors and biomarkers can be predicted and should monitor to identify the development of these toxicities. Several patient-related factors can influence the risk and severity of toxicities in CAR T-cell therapy. These include pre-existing comorbidities, age, disease burden, performance status, and prior treatments. Patients with a higher disease burden or compromised organ function may be more susceptible to toxicities [22.] Based on the design and characteristics of CAR T cells it impact the occurrence of toxicities. Factors such as the choice of target antigen, CAR construct, T-cell phenotype, and persistence of CAR T cells can influence the risk of toxicities [23]. High-affinity CARs or CARs targeting antigens expressed on normal tissues may increase the likelihood of off-target toxicities [22]. CRS can observed after CAR T-cell therapy. Biomarkers such as interleukin-6 (IL-6), interferon-gamma (IFN-γ), C-reactive protein (CRP), and ferritin have been studied to predict and monitor the onset and severity of CRS [23]. ICANS can be predicted by interleukin-1 receptor antagonist (IL-1Ra), soluble IL-2 receptor alpha (sIL-2Rα), and cytokines like IL-6, IL-8, and IL-15 and other Genetic and genomic factors of both the patient and the CAR T cells themselves have been investigated as potential predictors of toxicities because of Polymorphisms in genes involved in immune responses and inflammation have been studied for their association with the development of toxicities. [23,24] . Genomic profiling of CAR T cells may also provide insights into their potential to cause off-target toxicities.

Advances in toxicity management

Efforts are being made to develop risk stratification models to identify patients at higher risk of developing toxicities. These models consider factors such as disease characteristics, patient-related factors, and CAR T-cell product attributes. Proactive management can also done by early recognition and close monitoring of toxicities allow for timely intervention. Implementing proactive management protocols, includes standardized grading systems, that facilitate early intervention and appropriate escalation or initiation of treatment [34].

Gene editing and Synthetic receptors

Gene editing technologies, particularly CRISPR/Cas9, have revolutionized the field of genetic engineering and hold significant potential for enhancing the safety profile of CAR T-cell therapy. Alongside gene editing, the use of synthetic receptors presents an exciting avenue for further improving the therapeutic applications of CAR T-cell therapy.

In Gene editing technologies, such as CRISPR/Cas9, enable precise modifications of the genome by targeting specific DNA sequences. CRISPR/Cas9 utilizes a guide RNA molecule to direct the Cas9 enzyme to the target site, where it introduces double-stranded breaks in the DNA [37]. This allows for the addition, deletion, or modification of specific genes that can be used to enhance the safety and efficacy of CAR T cells.

I. **Knocking out endogenous T-cell receptors (TCRs):** By disabling the expression of TCRs using gene editing techniques, potential off-target toxicities caused by TCR recognition of non-target antigens can be minimized [37].

II. **Inserting safety switches:** Gene editing can be employed to introduce safety mechanisms, such as suicide genes, into CAR T cells. These safety switches allow for the elimination of CAR T cells in case of severe toxicity or adverse events.

III. **Enhancing persistence and anti-tumor activity:** Gene editing can be used to manipulate CAR T cells to enhance their persistence and anti-tumor activity. For example, disrupting specific genes that inhibit T-cell function can lead to enhanced CAR T-cell persistence and improved tumor clearance [38].

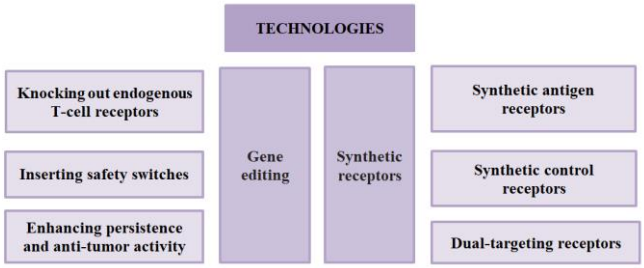

Fig.3 Gene editing and Synthetic receptors

Synthetic receptors offer a promising approach to augment the safety and specificity of CAR T-cell therapy. These receptors are designed to recognize alternative targets, distinct from the natural antigens targeted by CARs, to minimize off-target toxicities. Synthetic receptors can include:

I. **Synthetic antigen receptors:** These receptors are engineered to recognize synthetic antigens that are not expressed on healthy tissues, reducing the risk of toxicities associated with off-target recognition.

II. **Synthetic control receptors:** Control receptors are designed to respond to synthetic ligands that are absent in normal tissues but can be administered to modulate CAR T-cell activity. This provides an additional layer of control over CAR T-cell function.

III. **Dual-targeting receptors:** Dual-targeting receptors combine the recognition of a tumor-specific antigen with an additional target expressed on normal tissues. By requiring dual antigen recognition for CAR T-cell activation, the risk of off-target toxicities can be minimized.[39]

The development of gene editing technologies and synthetic receptors represents an exciting frontier in CAR T-cell therapy, allowing for enhanced safety, specificity, and control over CAR T-cell function.

Engineered CAR T-cell platforms

Novel engineering strategies have been developed to enhance the safety profile of CAR T-cell therapy, including switchable CARs, suicide gene systems, and conditional CAR expression. Switchable CARs, also known as controllable CARs, are designed to provide an additional layer of control over CAR T-cell activity. These CARs incorporate an external control mechanism that allows for the activation or deactivation of CAR signaling. Switchable CARs can be triggered by small molecules, antibodies, or other external stimuli. The goal is to improve the safety and controllability of CAR T-cell therapy by providing the ability to turn CAR signaling on or off as needed [40] another was Suicide gene systems, also known as safety switches, are engineered into CAR T cells to enable their elimination in case of severe toxicity or adverse events. These systems provide a safety mechanism to eliminate CAR T cells when necessary, enhancing the overall safety profile of CAR T-cell therapy. Suicide gene systems are typically activated by the administration of a specific drug or compound [41]. In Conditional CAR expression strategies aim to regulate the expression of CARs in a controlled manner. These approaches allow for the activation or suppression of CAR expression based on specific conditions or stimuli. By regulating the timing and intensity of CAR expression, conditional CAR expression strategies offer improved control over CAR T-cell activity [42].The development of these novel engineering strategies holds promise for enhancing the safety and controllability of CAR T-cell therapy [43].

Patient and caregiver education

Patient and caregiver education play a critical role in the successful implementation of CAR T-cell therapy and It is essential to emphasize the importance of education regarding the recognition and management of potential toxicities associated with CAR T-cell therapy. Detailed information about the potential side effects and toxicities associated with CAR T-cell therapy should be given. This includes common toxicities such as cytokine release syndrome, neurotoxicity, and hematologic toxicities. Patients and caregivers should maintain open communication with the healthcare team and report any concerning symptoms or changes in health status [44] . Emphasize the significance of regular monitoring and follow-up visits as recommended by the healthcare team. These visits are essential for the early detection of toxicities and prompt intervention. It is necessary to get clear instructions regarding the monitoring parameters and tests that need to be performed during the post-treatment period. This may include blood tests, vital sign monitoring, and specific assessments to evaluate organ function[45]. Connect patients and caregivers with support groups or organizations specializing in CAR T-cell therapy or the specific condition being treated. These resources can provide additional education, peer support, and guidance throughout the treatment journey. By empowering patients and caregivers with knowledge about potential toxicities and management strategies, they can actively participate in their care and contribute to the overall success of CAR T-cell therapy.[45]

CONCLUSION

CAR T-cell therapy holds tremendous potential in the treatment of hematological malignancies and solid tumors. Understanding the safety considerations and toxicities associated with CAR T-cell therapy is essential for optimal patient management. Ongoing research efforts aimed at refining toxicity management strategies and improving the safety profile of CAR T-cell therapy are crucial to ensuring its widespread and safe application.

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