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Balancing Efficacy and Safety: Modulating the Immune System with SUPRA CAR-T Cells for Cancer Therapy

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ABSTRACT
Cancer poses considerable challenges for effective treatment, notwithstanding the existence of various therapeutic options. Immunotherapy is a strategy that employs the immune system to detect and eradicate cancer cells. This entails the identification of specific antigens on cancer cells and the direction of T cells to recognize and eliminate them. Immunotherapy produces fewer side effects than traditional treatments such as chemotherapy. Nonetheless, it presents inherent safety risks, particularly the possibility of unintentional damage to healthy cells. In response to these concerns, developed SUPRA CAR as an advanced version of the original therapy, offering improved safety and efficacy. As an emerging technology, it possesses limitations that necessitate further examination.

KEYWORDS
SUPRA CAR-T Cells; Immunotherapy; Tumor Immune Evasion; Therapeutic Safety; Antigen Recognition

1 Introduction

Chemotherapy and radiotherapy are abiotic interventions that target tumor cells, yet traditional treatment often result in severe adverse effects. An alternative strategy is to enhance the body's innate immune system with the objective of destroying cancer cells, which is regarded as a safer approach. In this context, CAR has been the subject of considerable interest as a potential immunotherapy modality. In light of the limited efficacy of existing therapies that target immune evasion, a modified therapy, SUPRA CAR, has been developed with the objective of enhancing the ability of the immune system to recognize and destroy cancer cells. This therapy offers greater flexibility than traditional chimeric antigen receptor T-cell therapies. SUPRA CARs can be reprogrammed to target a variety of cancer types, which may result in lower side effect for patient. While SUPRA CAR-T therapy shows promise, a comprehensive assessment of its potential limitations is essential. The programmability of the system suggests that it may be a cost-effective and versatile technological advancement; however, the optimal dose of the therapy remains uncertain. Furthermore, additional research is necessary to strengthen the evidence base for clinical outcomes in specific populations.

2 Immune System Regulation and Cancer Therapy

In the earliest stages of cancer development, tumour cells utilize a multitude of sophisticated strategies to evade immune recognition and destruction. The prevailing approach is to modify protein processing and transport pathways, which ultimately impedes antigen delivery (Velilla, Rugeles and Chougnet, 2006). This alteration significantly impairs the capacity of cytotoxic T lymphocytes to recognize and destroy tumour cells, predominantly due to disruption of MHC molecular presentation. The avoidance of immune recognition of cancer cells signifies a significant disruption of tumour immune surveillance. In the event of insufficient detection, cancer cells will continue to proliferate, remaining unaware of the presence of the immune system. This process entails alterations in the expression levels of immunosuppressive molecules, including PD-L1 and PD-L2, during tumour development. These compounds are vital for the promotion of immunosuppression and the creation of a protective barrier for the tumour against immune responses (Sterner & Sterner, 2021). The capacity of cancer cells to proliferate in the face of immune surveillance underscores a glaring deficiency in the immune system. Nevertheless, the considerable emphasis placed on the enhancement of T-cell activity, there is a paucity of research into tumour 'escape pathways' (Anichini et al., 2020). These findings emphasize the necessity for a unified approach that addresses both tumour immune evasion mechanisms and T cell activation in the treatment and elimination of cancer. The primary objective of immunotherapy is to enhance the ability of the immune system to suppress tumour proliferation. First and second generation immunotherapies, including cytokine therapy and monoclonal antibodies, were rapidly superseded due to their lack of killing efficiency and severe adverse effects. The advent of third generation CAR-T cell therapy offers a promising alternative.

The genetically modified chimeric antigen receptor (CAR) is created to identify particular antigens on neoplastic cells. This approach specifically targets certain proteins, enabling CAR-expressing T cells to identify cancer cells, even when those cells impair the functionality of conventional T cells. CAR-T cell treatment entails the extraction of T cells from the

patient's peripheral blood, followed by their expansion in vitro. Synthetic biotechnology, including lentiviruses or retroviruses, facilitates the introduction of CAR constructs via single-chain variable fragments (scFv), hence augmenting tumour cell antigen recognition (Brentjens et al., 2013).

The transmembrane structural domain of the CAR is added to T cells via genetic engineering, facilitating the transmission of external signals into the cell. CAR-modified T cells overcome the limitations posed by a suppressed tumour microenvironment, where the major histocompatibility complex (MHC) expression is often diminished. Unlike natural T cells, CAR-T cells operate independently of MHC-mediated antigen presentation, enabling direct recognition and attachment to specific antigens on the surface of target tumour cells. When CARs bind to these antigens, they initiate an intracellular signalling cascade that activates T lymphocytes (Jiang et al., 2013).

However, clinical statistics reveal that most patients undergoing CAR-T cell therapy experience a significant decrease in white blood cell counts, particularly around lymph nodes. The immune response to B-cell antigens for common infections becomes impaired, resulting in inadequate antigen production and making patients more susceptible to illnesses like influenza (Anwar, Williams, & Paluri, 2020). This vulnerability arises from the MHC-independent activation of CAR-T cells, which leads to an uncontrolled attack on antigen-marked targets, resulting in the elimination of healthy cells that also express the targeted antigen. CD19 is used as a target antigen for CAR-T cells, but it is also expressed on healthy B cells. Clinical data from Schubert et al. indicate that more than 37% of B cells are depleted during treatment, which significantly impacts the immune system (Schubert et al. 2021).

In comparison to other forms of treatment, such as chemotherapy and surgery, the adverse effects associated with CAR have been relatively mild. However, the minimisation of these effects and the optimisation of treatment efficacy remain key areas of investigation.

3 SUPRA CAR Treatment

SUPRA CAR-T cell therapy represents an advancement over traditional CAR-T therapy by incorporating two main components: the universal receiver and the binder. This restructuring simplifies the construction process. Unlike conventional CAR-T therapy, which has a rigid configuration, the universal receiver in SUPRA CAR-T remains fixed to the T-cell which facilitating signal transduction similar to the traditional CAR, while also offering enhanced modularity. The binder, serving as the antigen-recognizing component, is a distinguishing characteristic of SUPRA CAR-T cell, setting it apart from traditional CAR-T therapies (Ellebrecht et al., 2016). Conventional CAR-T therapies utilize a fixed binder, which restricts the capacity of CAR-T cells to target various antigens. During treatment, tumour cells may alter gene expression or demonstrate lineage plasticity, leading to reduced or absent antigen expression. As a result, CAR-T receptors may fail to identify the antigen, thereby heightening the likelihood of cancer recurrence (Feucht et al., 2019). The SUPRA CAR system has been developed to tackle immune escape by incorporating multiple specificity or trigger switches, enabling the detection and targeting of various antigens present on tumour cells. The ability to identify various antibodies addresses the challenge of immune evasion in tumours with significant antigenic heterogeneity. The development of SUPRA CAR-T cells entails the use of variable binders, which are then administered to patients. If the antigens on tumour cells become unrecognizable, therapeutic efficiency can be significantly improved by isolating the binders and introducing new receptors that target alternative antigens.

In cases where tumour cells express inhibitory signals like PD-L1 which suppress T-cell activity, SUPRA CAR can also be adapted for use in NK cells and macrophages to alleviate the limitations of T-cells. Co-culture studies with NK cells and T cells showed a considerable increase in perforin and granzyme release against cancer cells following the introduction of the SUPRA CAR gene (Evripidis Lanitis et al., 2013). SUPRA CAR induced antigen-specific cytolysis by NK cells without needing specific antigens, thereby compensating for deficiencies in antigen presentation by T cells early in the treatment. This capability allows SUPRA CAR to effectively treat cancers with high antigenic heterogeneity, greatly enhancing the breadth and efficacy of the therapy. Clinical data show that 11% of children receiving CAR-T treatment experience relapse, and as treatment continues, the relapse rate increases to 24%. In contrast, the relapse rate in adults is lower, at 18% (Majzner & Mackall, 2018). patients who received SUPRA CAR-T cells showed a recurrence rate of 0%, which remained consistent throughout treatment (Boardman & Salles, 2023). These findings demonstrate that SUPRA CAR is more effective than traditional CAR, resulting in a notable improvement in treatment quality. It is essential to acknowledge that the provided statistics pertain solely to adult patients, rendering a comparison of CARs with SUPRA CARs in pediatric treatment clinics unfeasible.

Furthermore, SUPRA CAR therapy is a safer alternative to CAR therapy. In instances of severe adverse reactions in patients undergoing CAR therapy, a specific inducer is typically administered to activate a suicide gene implanted in the treated cells. However, this strategy inevitably results in the death of all treated cells, necessitating the generation of new CAR T cells if treatment is to be repeated. In contrast, the SUPRA CAR system mitigates adverse effects through the use of competitive inhibitory molecules that reduce immune cell activity by competing for active sites, thereby reducing the

need for immune cell reactivation in subsequent treatments (Fesnak, June, & Levine, 2016). The removal or inactivation of treated cells requires additional intervention, making the prevention of this effect the most effective strategy for mitigating off-targeting consequences and minimizing damage to normal cells. SUPRA CARs are engineered to be bispecific, employing three logic gates (AND, NOT, and NOT-AND) to modulate signalling (Cho, Collins, & Wong, 2018). The AND gate necessitates the binding of both CAR modules to the target antigen for activation, thereby ensuring that binding solely to normal cellular antigens does not trigger an immune response. The NOT gate activates CAR-T cells solely in the absence of a specific antigen, enabling selective avoidance of normal cells that express 'suppressor antigens'. The recent method combines two logic gates, allowing the receptor to identify two distinct antigens: tumour antigen A and normal cell antigen B. In contrast, the detection of solely antigen A results in an activation signal targeting the tumour cells, whereas the presence of antigen B safeguards normal cells from damage (Cho et al., 2021). Following a three-month course of SUPRA CAR treatment, patients exhibited an 11% depletion of B cells, while white blood cell counts remained within the normal range and other normal cells in the treated area remained at normal levels. In comparison to CAR, SUPRA CAR is associated with a reduced risk of adverse effects.

SUPRA CAR, as an enhanced version of CAR, addresses the deficiencies of CAR in terms of both efficacy and safety. However, it still has certain limitations, particularly in the management of advanced malignancies, where efficacy can be significantly reduced.

4 Discussion

SUPRA CAR, as a representative of immunotherapy, has been demonstrated to be an effective and safe modality for eliminating cancer cells. However, its therapeutic efficacy is diminished in advanced stages of cancer, particularly when malignant cells proliferate to form tumours. In data pertaining to the treatment of solid tumours, the efficiency of SUPRA CAR was observed to decrease by 65.3%, while its single use led to a 35.5% reduction in disease control and accelerated deterioration (Liu et al., 2022). This reduction in efficacy is due to the formation of solid tumours with dense stromal tissue in the middle and late stages of cancer, which creates a physical barrier that impedes T cell penetration or leads to their inactivation in the circulatory system or extra-tumoral region before reaching the target site, thus preventing effective anticancer activity.

In the middle and late stages of cancer, the efficacy of SUPRA CAR T cells is inadequate, as they can only eliminate cancer cells one by one, which is insufficient for complete eradication. As the number of cancer cells increases, the dosage of SUPRA CAR T cells injected into the body must also be increased, making dosage a crucial consideration in treatment. A correlation has been identified between the clinical response observed in patients and the dose of CAR-T cells injected. Patients who received SUPRA CAR at higher doses exhibited increased toxicity. Conversely, when patients were injected with up to 1 billion CAR-T cells, the toxins produced remained within normal ranges (Anand Rotte et al., 2022). However, as T cells began to proliferate, toxin levels exceeded the threshold, leading to adverse effects. Consequently, Anand Rotte et al. concluded that there was no correlation between dose and toxicity and that adverse effects could be mitigated by controlling T-cell proliferation. Notably, this trial was conducted on solid tumours concentrated in organs such as the lungs and stomach, while blood cancers were not included in the study. Unlike single-organ treatment, toxins produced during treatment for blood cancers are distributed throughout various organs, necessitating separate analysis of the medicinal dose for solid cancers. In the trial conducted by Lu and Jiang, an overdose of SUPRA CAR for the treatment of blood cancers resulted in an increase in the objective remission rate (ORR), indicating that the patient's cancer exhibited signs of improvement. However, levels of toxins in the blood were elevated above the normal threshold, and 56% of the patients experienced adverse reactions, 22% of which were serious. The use of an excessive number of SUPRA CARs has been identified as a significant risk factor for adverse effects and even death (Lu and Jiang, 2022). Consequently, the dosage must be meticulously calibrated according to the specific type of cancer in order to effectively manage disease progression in the future.

The efficacy of SUPRA CAR in treating solid cancers is further limited by the specialized microenvironment within solid tumours, which are highly heterogeneous and contain diverse cellular populations expressing distinct antigens. Consequently, despite the multiple antibody recognition mechanisms of SUPRA CAR, its efficacy is inevitably diminished. In a study involving 100 solid cancer patients treated with SUPRA CAR, the remission rate was 11.8%, while the condition of the remaining patients continued to deteriorate (Hou et al., 2019). Although SUPRA CAR is capable of eradicating cancerous cells with the same efficacy as other treatments, the lengthy process may prove fatal for patients with advanced disease. Therefore, SUPRA CAR cannot be employed as a primary method for eradicating solid tumours. However, its utilization in conjunction with alternative approaches holds promise for exploring new avenues in cancer therapy.

One of the most common methods for treating solid cancers is surgery. A significant complication of surgery is the inability to completely remove cancer cells, which can lead to recurrence. When patients were treated with SUPRA CAR

following surgery, the number of abnormal cells (potentially cancerous cells) remained within normal limits for six months, and tumours showed no signs of recurrence (Chao et al., 2023). The combination of SUPRA CAR and chemotherapy has also demonstrated effectiveness. When the tumour microenvironment is disrupted by chemotherapy, SUPRA CAR is able to eliminate remaining cancer cells, thereby opening new avenues for treatment. The disruption of the tumour microenvironment by chemotherapy resulted in the elimination of cancer cells by SUPRA CAR at a rate 67% higher than that observed in the absence of chemotherapy. Furthermore, the combination of chemotherapy and SUPRA CAR T-cells demonstrated a 33% higher rate of cancer cell elimination compared to chemotherapy alone (Hallaj et al., 2019). However, the chemicals used in chemotherapy can sometimes damage the structure of SUPRA CAR, leading to its inactivation. A reduction of 49% in SUPRA CAR T-cells was observed within six months of chemotherapy, while 23% of SUPRA CARs exhibited disruption of their binder, resulting in a decline in antibody recognition (Truong et al., 2021). Therefore, more effective combination therapies will need to be explored in the future. While SUPRA CAR has demonstrated limited effectiveness in treating advanced solid tumours, results from combination therapies suggest that further development of this approach is warranted.

It also becomes equally imperative to highlight the general lack of clinical evidence on the appropriateness of SUPRA CAR in the elderly. The immune systems in an elderly patient are not as strong as in any younger patient, and there might be greater chances of side effects if the treatment is not given precisely. As a result, most of the aged patients have not yet been subjected to SUPRA CAR treatment due to the inadequacy of study findings from this group. In the 2024 trial, three elderly patients out of 12 experienced a relapse and died within three months of SUPRA CAR infusion (Menez et al., 2024). It is, therefore, of high relevance that the safety and efficacy of SUPRA CAR therapy be assessed in elderly patients to determine its applicability and whether or not further studies will be warranted.

5 Conclusion

Immunotherapy has made notable progress in the domain of cancer therapy, with SUPRA CAR emerging as a promising approach for cancer cell growth. Nevertheless, there persists a discrepancy between its efficacy and that of more established treatments. Consequently, there is a necessity to enhance the efficiency of this therapy or integrate it with other treatment modalities as a future objective in cancer therapy.

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