International Immunopharmacology 70 (2019) 498–503

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Chimeric antigen receptor T cell therapy and other therapeutics for malignancies: Combination and opportunity☆

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ARTICLE INFO

Keywords:
CAR-T therapy
Combination immunotherapy
Malignancies

ABSTRACT

Chimeric antigen receptor T (CAR-T) cell therapy provides possibility for the treatment of malignancies since clinical trials have shown that CAR-T therapy has a significant anti-tumor effect. Although many efforts have been made to improve the efficacy and reduce the side effects of CAR-T therapy, there are still many problems to solve. With the rapid development of this field, combination immunotherapy has been proved to improve the efficacy of CAR-T therapy. Studies have shown that radiotherapy, chemotherapy, oncolytic virotherapy, BTK inhibitors and immune checkpoint blockade-based therapy may further enhance the efficacy of CAR-T therapy while CRISPR/Cas9 technology and IL-1 blockade may improve the safety. In this review, we summarized the advantages and the mechanisms of the combination immunotherapy based on CAR-T cell therapy.

1. Introduction

Chimeric antigen receptor T (CAR-T) cell therapy is a new strategy for cancer treatment by genetically modifying T cells in vitro, which can specifically identify and kill tumor cells [1,2]. CAR-T cells recognize the tumor-associated antigens (TAA) independent of major histocompatibility complex (MHC) restriction, broadening the clinical application [3]. The CAR consists of four components: a tumor associated antigen-binding domain which is called single-chain variable fragment (scFv), an extracellular spacer domain, a transmembrane domain and an intracellular signaling domain. CAR-T technology has undergone four generations with the continuous development of genetic engineering technology. The first-generation of CARs was designed to contain only one intracellular signal region [4]. The first generation of CAR has a weak anti-tumor effect. On the basis of the first-generation of CARs, the second-generation of CARs enhances its anti-tumor effect by joining costimulatory domains CD28 or 4-1BB (CD137) [5]. The third-generation of CARs is composed of activated domains and multiple costimulatory domains, such as CD27, CD28 and OX40 [6–8]. The join of these domains not only enhances the ability of CAR-T cells to specifically recognize TAA and bind to TAA, but also significantly increase the killing effect on tumor cells. To further optimize the effect of CAR-T therapy, the forth-generation of CARs was further developed in many ways, such as adding suicide genes and expressing IL-2 [9,10].

Though there are four generations of CAR design so far, the second-generation of CARs is the most commonly used therapy because of its stable activity, controlled side effect and most therapeutic experience in the treatment of malignancies.

Most of the clinical trials of CAR-T cell therapy are adopted to treat CD19 positive hematological tumors such as B cell acute lymphoblastic leukemia(B-ALL), chronic lymphocytic leukemia (CLL) and B cell non-Hodgkin lymphoma(NHL). Recently, studies have shown high complete remission (CR) rates of 90% in treating acute lymphoblastic leukemia (ALL) with CD19 CAR-T therapy both in children and adults [11]. This impressive result brings about multiple CAR-T therapies targeting to many other hematological tumors antigens, such as CD20 [12,13], CD22 [14] and CD30 [15]. Efforts have also been made in identifying targets for solid tumors and improving the efficacy of treating solid tumors. Although it seems more difficult to treat solid tumors than to treat hematological malignancies using CAR-T therapy for various reasons, achievements have already been obtained in many kinds of solid tumors, such as pancreatic cancer [16] and diffuse intrinsic

☆ The authors have declared that no conflict of interest exists.

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https://doi.org/10.1016/j.intimp.2019.01.010
Received 18 September 2018; Received in revised form 7 January 2019; Accepted 7 January 2019
Available online 13 March 2019
1567-5769/

pontine glioma (DIPG) [17]. The distinct antitumor response of CAR-T therapy has made it a promising strategy in reducing the tumor patients' mortality and prolonging the tumor patients' survival.

Unfortunately, there are still some problems limiting chimeric antigen receptor T cell therapy. The migration of T cells to the solid tumors is suppressed by the immunosuppressive signaling pathway composed of the chemokines secreted by solid tumors. The immunosuppressive tumor microenvironment (TME) recruits immunosuppressive cells including myeloid cells and fibroblasts [18]. The infiltration of T cells into the solid tumors is inhibited by the fibrotic extracellular matrix consisting of the immunosuppressive cells [19]. In the case of B-ALL, CAR-T cell therapy causes rapid and sustained clinical response, but it is also accompanied by acute toxicity, which can be very serious, and even fatal. Cytokine release syndrome (CRS) and neurotoxicity caused by CAR-T therapy are considered as the most life-threatening reactions. In multiple clinical trials of CAR-T immunotherapy, the toxicity of target non tumor (on-target, off-tumor) has also been reported, which can induce the damage of normal tissue expressing the target antigen [20,21]. Improving the safety of CAR-T cells is the key to the successful application of CAR-T therapy. CAR-T cell therapy for solid tumors has met more problems than the treatment for hematological malignancies [22], due to the great differences between hematologic malignancies and solid tumors. Among these differences, heterogeneity and physical immunosuppressive factors of solid tumor should be taken into consideration. Many strategies have been developed to improve the safety and efficacy of CAR-T cell therapy in the treatment of malignancies including hematological malignancies and solid tumors. It has been reported that many other therapeutics may further enhance the safety and efficacy of CAR-T therapy [23,24]. In this review, we will mainly discuss the prospect of the combination of CAR-T cell therapy and other therapeutics for malignancies.

1.1. The combination of CAR-T cell therapy and radiotherapy/ chemotherapy

For CAR-T therapy, the persistence of T cells is positively related to the efficacy of the therapy. Depletion of lymphocytes before infusion of CAR-T cells is an effective way to increase the persistence of CAR-T cells and reduce the tumor burden. Radiotherapy, which is a common therapy for malignant tumors, can not only kill tumor cells directly, but also induce tumor-specific immune responses. Pre-clinical studies have shown that radiotherapy could increase the expression of tumor specific antigen, reduce side effects and improve the efficacy of anti-tumor immunotherapy [23,24]. Also, pre-clinical studies have indicated radiotherapy could enhance the recruitment of activated T cells by increasing the secretion of chemokines, such as CXCL9, CXCL10 and CXCL16 [25].

Fludarabine and cyclophosphamide are two commonly used chemotherapeutic agents to clear lymphocytes before administration of CAR-T cells. It has been indicated that chemotherapy could improve CAR-T therapy by making new niches for the expansion of CAR-T cells by clearing the resident cell populations [26,27]. In addition, chemotherapeutic drugs could eliminate immunosuppressive cells.

The combination of radiotherapy or chemotherapy with CAR-T cell therapy is more efficient than the therapy of CAR-T cells alone, which provides a promising strategy for the potentiation of CAR-T therapy.

1.2. The combination of CAR-T cell therapy and immune checkpoint blockade-based therapy

Immunological checkpoints refer to some inhibitory signaling pathways in the immune system that prevent tissue damage by regulating the persistence and intensity of immune responses in peripheral tissues, and participate in maintaining tolerance to autoantigens [28]. Inhibition of T cell activity by the inhibitory signaling pathway of the immunological checkpoint leads to the tumor escape from immune surveillance [28,29]. Therefore, a new class of anti-tumor drugs that inhibit immune checkpoints and unleash anti-tumor immunity has been developed. Among such drugs, those targeting cytotoxic T-lymphocyte antigen 4 (CTLA4) [30], programmed cell death 1 (PD-1) [31], and programmed cell death ligand 1 (PD-L1) have emerged in clinical trials [32].

Pre-clinical studies have shown that it is a promising strategy to reverse the immunosuppressive tumor microenvironment with immune-checkpoint blockade to enhance the therapeutic effect of CAR-T therapy in malignancies, especially solid tumors [33]. Evidence has shown that the administration of a PD-1 blocking antibody or a PD-L1 blocking antibody could significantly increase the therapeutic activity of CAR-T cells by partially rescuing effector functions of M28z and reducing tumor burden significantly [34,35]. Nevertheless, it is worth noting that only high doses of antibody could take effect in improving the antitumor efficacy of CAR-T cells. Besides, the efficacy of the antibody is transient and repeated administration is required to rescue the activity of CAR-T cells and inhibit tumor progression [36,37]. To overcome these shortcomings, CAR-T cells were genetically engineered to express a PD-1 dominant negative receptor (PD-1 DNR) on the surface. Compared with the administration of PD-1 antibody, the intrinsic PD-1 checkpoint blockade in CAR-T cells has more sustainable effect and lower toxicity, providing opportunities to improve the efficacy of CAR-T therapy [38]. With the rapid development of this field, many novel strategies of the combination of CAR-T cell therapy and immune checkpoint blockade-based therapy have emerged. For example, a chimeric switch-receptor targeting PD-1 has been engineered, which is comprised of the PD-1 extracellular domain and the transmembrane and cytoplasmic signaling domains of CD28 [39].

Although PD-1 blockade has been proved to enhance the activity of CAR-T cells, some mice treated with PD-1 DNR CAR T cells have been found to relapse after treatment [34]. This indicates that there are still many immunosuppressive mechanisms in the tumor microenvironment to overcome. The combination of CAR-T cell therapy and immune checkpoint blockade-based therapy needs further optimization to treat malignant tumors, especially solid tumors.

1.3. The combination of CAR-T cell therapy and oncolytic virotherapy

The oncolytic virus (OVs) is a kind of tumor-killing virus which can kill tumor cells in a specific manner, and produce and release new virus progeny within the affected tumor cells [40]. The released viruses can further infect other tumor cells, thus achieving the ideal therapeutic effect. Mechanistically, oncolytic virus can not only selectively kill tumor in a direct fashion, but also has the potential to enhance the antitumor effect of other cancer treatments by stimulating the immune response of human body. Recent clinical studies of OVs have shown that many of OVs, especially those expressing granulocyte macrophage colony-stimulating factor (GM-CSF), can effectively induce the antitumor immune response without obvious toxicity [41,42].

OVs primarily function in three stages of T cell therapy (T cell priming, infiltration of T cells, and the engagement of T cells and tumor cells) [43–45]. The initiation of T cell response requires identification of specific epitopes, in which the processing of antigen presentation is necessary. Antigen presentation is usually suppressed in cancer. Oncolytic virus can expose a large number of tumor-related antigens through the lysis of cancer cells and generate a immune microenvironment, thus promoting the presentation and recognition of tumor-related antigens during T cells priming [46]. Oncolytic viruses are expected to promote the infiltration of T cells which plays an important role for the prognosis of cancer patients through several underlying mechanisms. It has been established that viral infection induces the type 1 interferons (IFNs) and stimulates chemokines which can recruit T cells [47]. Additionally, OVs can induce the production of inflammatory cytokines which can increase the expression of selectin on endothelial cells to provide a significant signal for the infiltration of

T cells [48]. The genetically engineered OVs can be activated by the signal pathway with immunosuppressive effect, such as WNT/β-catenin pathway, promoting the replication and anti-tumor effect of the viruses [49]. The OVs can also be engineered to directly recruit T cells by encoding T cell chemoattractants despite the lack of chemokines in the tumor microenvironment [50]. After T cells infiltration, the engagement of T cells and tumor cells is critical for further lysis of tumor cells. Nevertheless, the immunosuppressive cells and molecules, such as IL-10, TGFβ and IDO, can block the engagement of T cells to tumor cells. The application of OVs can activate pro-inflammatory T helper 1, thereby altering the immunosuppressive tumor microenvironment. Furthermore, OV is also found to directly kill inhibitory cells [51]. Tumor cells can avoid the recognition of T cells by downregulating pathways related to antigen presentation and major histocompatibility complex (MHC) class I [52–54]. OVs can reverse these effects perhaps by inducing type I interferon production [54].

In short, OVs can help T cells break through the immune barrier to enhance the efficacy of CAR-T therapy in multiple ways. Oncolytic virotherapy is expected to significantly enhance the therapeutic effect of CAR-T therapy without additional toxicity, and thus, there may be a large number of studies and clinical trials focused on the combination of these two therapies to improve the treatment of cancer patients in the near future.

1.4. The combination of CAR-T cell therapy and BTK inhibitors

BTK (Bruton's tyrosine kinase), a Tec family kinase present in the cell membrane and nucleus, is an important part of the B cell receptor (BCR) signaling pathway and is important in B cell maturation and the regulation of cellular processes including cell differentiation and signal transduction [55]. Studies have found that BTK is highly expressed in B cell malignancies, indicating that inhibition of BTK may be an effective way for the treatment of B cell malignancies [56]. Ibrutinib (PCI-327 65), a covalent irreversible inhibitor of BTK which has high selectivity for BTK, has aleady been approved by the FDA and EMA for treatment for chronic lymphocytic leukemia [57]. Pre-clinical studies have shown that combination of BTK inhibitor ibrutinib and CART19 is more effective in killing MCL cell lines than single therapy [58]. In addition, in vivo experiments in mice showed that the combination of these two therapies could improve the antitumor activity and reduce the recurrence rate of single therapy [58]. BTK inhibitors may increase the efficiency of CAR-T for the following reasons. Ibrutinib could enhance the overall anti-tumor effect by inhibiting AKT signaling, reducing cell terminal differentiation, and increasing the proportion of memory CART19 cells [59]. Also, ibrutinib can effectively mobilize tumor B cells to immerse in peripheral blood, makeing these cells destroyed by circulating CAR-T cells [59].

Although there may be some adverse events caused by drugs in the combination of BTK inhibitors and CAR-T therapy, such as bleeding and atrial fibrillation, the combined therapy may be a novel approach to treat patients with B-cell malignancies.

1.5. The combination of CAR-T cell therapy and CRISPR/Cas9 technology

Clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated (Cas) protein 9 system has become a popular genome engineering tool in biology and therapy because of its ability to edit genomes of various organisms precisely [60,61]. CRISPR/Cas9 gene editing technology provides a novel strategy to generate PD-1-deficient CAR-T cells and to knock out HLA to make a CAR universal.

Evidence has shown that the PD-1-deficient CAR-T cells based on Cas9-edited technology had better therapeutic efficacy because the deficiency of PD-1 promoted CAR-T cells to kill tumor cells and enhanced clearance of PD-L1$^+$ tumor xenografts [62]. The successful construction of Cas9-edited PD-1 deficient CAR-T cells brings about the further applications of Cas9 gene editing technology in CAR-T therapy.

To date, most CAR-T therapies require costly and time-consuming autologous adoptive cell transfer. For some patients, it is not easy to obtain sufficient healthy T cells. Therefore, how to use T cells harvested from one healthy donor to meet the clinical needs of multiple patients by generating a large number of CAR-T cells is a difficult problem to solve. To treat many patients with allogeneic CAR-T cells, it is necessary to ensure that adoptive cells do not attack the patient's healthy cells and to minimize their immunogenicity to avoid being attacked by host cells. CRISPR/Cas9 technology could solve these two problems by eliminating the αβ T-cell receptor (TCR) on allogeneic CAR-T cells and removing human leukocyte antigens class I (HLA-Is) on CAR-T cells [63,64]. The disruption of endogenous TCR and B2M genes based on CRISPR/Cas9 reduced alloreactivity and didn't cause graft-versus-host disease. Besides, the CRISPR/Cas9 gene-edited CAR-T cells showed the same anti-tumor activity as the unedited ones. In the absence of TCR and B2M genes, the disruption of PD1 gene by Cas9-edited technology could further enhance the efficacy of CAR-T allogeneic immunotherapy [63,64]. In addition, CRISPR/Cas9 gene-editing technology could provide potential better efficacy for CAR-T therapy in malignancies by disrupting antigens on normal cells. For example, in acute myeloid leukemia (AML), the overexpressed myeloid antigen CD33 in tumor cells is a tumor-associated antigen for CAR-T therapy [65]. However, the expression of CD33 in normal cells leads to severe damage to normal bone marrow by CD33-CAR T cells therapy. CRISPR/Cas9 could make CD33 on cancer cells surface the only target of CD33-CAR T cells by disrupting CD33 from hematopoietic stem cells, thus leading to less side effects of CD33 targeting CAR-T therapy.

Although the combination of CAR-T therapy and CRISPR/Cas9 technology is still in pre-clinical stage at present, it is a promising way to improve the treatment of tumor patients. CRISPR/Cas9 gene-editing technology could knock out multiple genes that are harmful to CAR-T cells therapy at once, thus reducing side effects and improving the efficacy of CAR-T therapy. The CRISPR/Cas9 technology could also provide the possibility of CAR-T allogeneic immunotherapy. Although there remain many problems for the combination of CAR-T therapy and CRISPR/Cas9 need to be solved, such as how to improve safety and accuracy, the development of gene editing technology may further improve the status of CAR-T therapy and provide effective CAR-T therapies benefiting on more tumor patients.

Combination therapies aimed at avoiding toxicities.

Although CAR-T cell therapy has shown impressive results in the treatment of malignant tumors, especially hematologic malignancies, it has many side effects. Cytokine release syndrome (CRS) and neurotoxicity are the most serious side effects of CAR-T therapy [66]. The clinical manifestations of CRS are chills, fevers, nausea, headache, hypotension, rash and other symptoms [66]. Severe CRS and neurotoxicity can lead to death, making it important to evaluate and control them in clinical practice [67]. Recently, by simulating the conditions of CRS in mouse models, studies have revealed that the inflammation-related molecules IL-1 and IL-6 derived from macrophages play an important role in the pathogenesis of neurotoxicity and CRS. The addition of IL-1 blockade could avoid both CRS and neurotoxicity while IL-6 blockade could simply prevent CRS [68,69]. Anakinra, a drug that blocks the secretion of IL-1, could significantly improve the safety and efficacy of CAR-T therapy by preventing CRS and neurotoxicity.

Although it has been indicated that IL-1 blockade could improve the safety of CAR-T therapy, further clinical trials are required for the combination of IL-1 blockade and CAR-T therapy. For future research, it will be a promising strategy to design CAR-T cells that could produce and secrete IL-1 antagonists.

2. Discussion

CAR-T cell therapy has made progress in the treatment of both hematological malignancies and solid tumors in the past few years, however it is still faced with many challenges [68,70]. T cell exhaustion

and the immune barrier both limit the efficacy of CAR-T therapy, while severe adverse events including CRS and neurotoxicity reduce the safety of the treatment process [66,70]. Autologous adoptive cell transfer is expensive and time-consuming, but allogeneic cell transfer may cause serious side effects, such as graft-versus-host disease (GVHD) [71]. In addition to the above problems, there are more difficult problems in the treatment in solid tumors with CAR-T therapy because of the immunosuppressive signaling pathways and immunosuppressive tumor microenvironment in solid tumors [46,47,70]. Faced with these problems, the combination therapy based on CAR-T therapy may provide feasible solutions. Relevant studies have shown that radiotherapy, chemotherapy, oncolytic virotherapy, immune checkpoint blockade-based therapy, CRISPR/Cas9 technology and IL-1 blockade may improve the safety and efficacy of CAR-T therapy through different mechanisms.

It is critical to determine which patients need combination therapy and choose which kind of combination therapy in the treatment for tumor patients. The clinical manifestations are diverse between tumor types and patients, so the combination immunotherapy needs to be personalized [72]. Patients who benefit from a single treatment and do not need combination therapy should not be given combination therapy to avoid the toxicity of combination therapy. For patients who need to be treated with combination therapy, the kind of combination therapy should be determined according to their own conditions, thus improving the therapeutic effect and minimizing toxicity [73]. Radiation therapy, chemotherapy and BTK inhibitor may be useful for patients with low efficiency in CAR-T therapy. For solid tumor patients, the application of immune checkpoint blockade or oncolytic virotherapy may be good ways to improve the therapeutic effect of CAR-T therapy. For patients with CRS and neurotoxicity after CAR-T therapy, the adopt of IL-1 inhibitors may be helpful in avoiding these toxicities. CRISPR/CAS9 technology can promote the development of CAR-T therapy in many ways, such as making CAR-T universal and knocking out the genes that block CAR-T therapy. In addition, the improvement of CAR design is also required in further research for the successful combination therapy.

In conclusion, the combination of CAR-T cell therapy and other therapeutics is a promising strategy for malignancies. The new combination immunotherapy deserves further studies to enhance the antitumor effect and avoid side effects.

Advantages of combined therapy	CAR T cell combinatorial strategies	Ref
Enhance the efficacy of CAR-T therapy	CAR-T + radiotherapy/chemotherapy	[23,24,26,27]
	CAR-T + immune checkpoint blockade-based therapy	[34,35]
	CAR-T + oncolytic virotherapy	[43]
	CAR-T + BTK inhibitors	[59]
Improve the safety of CAR-T therapy	CAR-T + CRISPR/Cas9 technology	[62,63]
	CAR-T + IL-1 blockade	[68,69]

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