

Combination therapy: A feasibility strategy for CAR-T cell therapy in the treatment of solid tumors (Review)

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Abstract. Chimeric antigen receptor (CAR) T-cell therapies have been demonstrated to have durable and potentially curative therapeutic efficacies in patients with hematological malignancies. Currently, multiple clinical trials in CAR-T cell therapy have been evaluated for the treatment of patients with solid malignancies, but have had less marked therapeutic effects when the agents are used as monotherapies. When summarizing relevant studies, the present study found that combination therapy strategies for solid tumors based on CAR-T cell therapies might be more effective. This review will focus on various aspects of treating solid tumors with CAR-T cell therapy: i) The therapeutic efficacy of CAR-T cell monotherapy, ii) the feasibility of the CAR-T cell therapy in conjunction with chemotherapy, iii) the feasibility of CAR-T cell therapy with radiotherapy, iv) the feasibility of CAR-T cell therapy with chemoradiotherapy, and v) the feasibility of the combination of CAR-T cell therapy with other strategies.

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1. Introduction

Chimeric antigen receptor (CAR) T-cell therapy has emerged as a potentially curative therapy in the treatment of a broad range of malignancies (1). CARs generally consist of an extracellular single-chain variable fragment (scFv) of an antibody for target recognition, a transmembrane domain fused with co-stimulation signaling domains, such as CD28 or 4-1BB, and a CD3 ζ signaling domain to provide T-cell activation signals (2-4). Additionally, antigen recognition by CAR-T cells occurs in a major histocompatibility complex (MHC)-independent manner, which helps to overcome tumor immune evasion by the down-regulation of MHC molecules on the cell surface (5,6).

To date, even though CAR-T cells have demonstrated dramatic efficacy in patients with hematological malignancies, particularly in treating B-cell hematologic malignancies with CD19-specific CAR T-cells (7,8), the clinical application of CAR-T cells in the treatment of solid tumors has not yet been successful, which raises questions about the feasibility of CAR-T cell therapy for the treatment of solid tumors (9-11). Nevertheless, the present authors wanted to determine whether CAR-T cell therapy has a curative effect on solid tumors and which is the best way to correctly establish the role of CAR-T cell therapy in the treatment of solid tumors. In the present review, the feasibility of combining CAR-T cell therapy with other treatments, such as chemotherapy, radiotherapy, chemoradiotherapy and other immunotherapy strategies is illustrated (Fig. 1).

2. Therapeutic efficacy of CAR-T cell monotherapy in the treatment of solid tumors

Most clinical studies have shown that CAR-T cell monotherapy had insufficient efficacy to treat solid tumors. For example, in a clinical study from Lamers *et al* (12) on renal carcinoma patients with first-generation CAIX-specific CAR-T cells, they observed low clinical response rates (9,12). Similar effects have been observed in neuroblastoma patients treated with first-generation CD171-specific CAR-T cells (13), patients with ovarian cancer

treated with epidermal growth factor receptor (EGFR)-specific CAR-T cells (14) or α -folate receptor (FR)-specific CAR-T cells (15), and colon cancer patients treated with third-generation Her-2-specific CAR-T cells (16). A study from Louis *et al.* (17) reported that of neuroblastoma patients who received GD2-specific CAR-T cells, some did not respond at all, and some exhibited disease progression during or following treatment.

Although clinical data have revealed that the efficacy of CAR-T cell monotherapy in the treatment of solid tumors is limited, the present authors still consider CAR-T cell therapy as a potential therapy to treat solid tumors. The full potential of CAR-T cell therapy is not understood due to the main reasons for the failure of CAR-T cell monotherapy to treat solid tumors, which are as follows. Firstly, current patients in CAR-T cell therapy clinical trials are patients who have received many other treatments that have not worked. The patients' physical conditions are already poor. Secondly, it is not possible for heavy-burden solid tumors to be eradicated by CAR-T cell monotherapy. Therefore, greater value and better results might be seen with CAR-T cell therapy in treating solid tumors if patients with early-stage-cancer were selected and CAR-T cell therapy was combined with other therapies, such as chemotherapy, radiotherapy, surgery and other immunotherapy strategies.

3. Feasibility of using CAR-T cell therapy with chemotherapy for treatment of solid tumors

Preclinical and clinical studies have demonstrated that CAR-T cell therapy and chemotherapy alone are not sufficient to eradicate large solid tumors or metastasis, resulting in recurrence or refractory disease (9,18). A large amount of data has suggested that the combination of chemotherapy with CAR-T cell therapy should be attempted, and novel combination strategies should show potential synergistic effects in practice in the future (19,20).

Chemotherapy is able to improve the efficacy of CAR-T cell therapy. Recent studies have indicated that a number of chemotherapeutic agents, including cyclophosphamide, doxorubicin, oxaliplatin, fluorouracil and gemcitabine, are not only able to reduce tumor burden but also have considerable immunomodulatory effects (21-23). It has been reported that the combination of immunotherapy with chemotherapy may achieve a more prominent curative effect than monotherapy (20). In the following section, the pathways by which chemotherapeutic agents induce the immune response, which should promote the curative effect of T-cells, are reviewed and then the feasibility of the combination of CAR-T cells with chemotherapy is analyzed (Fig. 2).

Chemotherapeutic agents are able to sensitize tumor cells to immunotherapy. Studies have indicated that mannose-6-phosphate receptors on tumor cell surfaces are upregulated following treatment with certain chemotherapeutic agents, which makes it easier for granzyme B released by cytotoxic T lymphocytes (CTL) to permeate tumor cells, sensitizing tumor cells to immunotherapy in an autophagy-dependent manner (24-26). Apart from this, one preclinical case of ErbB-retargeted T-cells combined with carboplatin demonstrated that treatment with low doses of the chemotherapeutic agent carboplatin was able to sensitize tumor cells to specific-ErbB

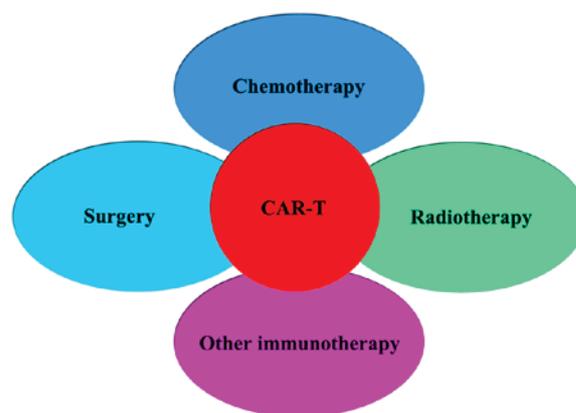


Figure 1. Combination strategies based on CAR-T. The effects of chemotherapy, surgery, radiotherapy and other strategies are expected to be complementary or synergistic, and may remarkably improve the efficacy of antitumor therapy in the future. CAR-T, chimeric antigen receptor T-cell.

CAR T-cell-mediated cytotoxicity and enhance the efficacy of the antitumor immunotherapy (27,28). The mechanisms of increasing sensitivity to immunotherapy following treatment with certain chemotherapeutic agents are not fully understood, but in other studies, the enhanced therapeutic efficacy was also observed following combination therapy (29).

Chemotherapeutic agents are able to improve tumor antigen recognition and presentation. Research has indicated that certain chemotherapeutic agents, such as taxanes (docetaxel and paclitaxel) and vinca alkaloids (vinorelbine and vinblastine), were able to facilitate tumor cell recognition by increasing exposure to calreticulin and killing tumor cells, thereby releasing large quantities of tumor antigens (30). In addition, studies have indicated that a number of chemotherapeutic agents were able to improve tumor antigen presentation. The main pathways are as follows. Firstly, autophagy induced by some chemotherapeutic agents stimulates tumor cells to release ATP, which increase the recruitment of dendritic cells (DCs) and T lymphocytes to infiltrate the tumor bed for tumor antigen presentation (21,31-33). Secondly, it has been reported that the dying tumor cells induced by chemotherapeutic agents release damage-associated molecular patterns (DAMPs), such as high-mobility group box 1 (HMGB1), which could be recognized by Toll-like receptor 4 to promote DC maturation and activation, enhancing the antitumor T-cell response (34-37). Thirdly, chemotherapeutic agents induce tumor cells or stromal cells to generate endogenous type I interferons (IFNs) and increases the exogenous type I IFNs, which can activate DC and induce T cell cross-priming, leading to tumor control (20,22,38).

Certain chemotherapeutic agents are able to inhibit suppressive immune cells. It has been confirmed that certain chemotherapeutic agents (doxorubicin, fluorouracil, gemcitabine, cyclophosphamide and docetaxel) are able to selectively inhibit immunosuppressive cells (regulatory T cells and myeloid-derived suppressor cells) to enhance the efficacy of antitumor immunotherapy (39). Studies have revealed that certain immunosuppressive cells are more sensitive than T-cells to some chemotherapeutic agents, and

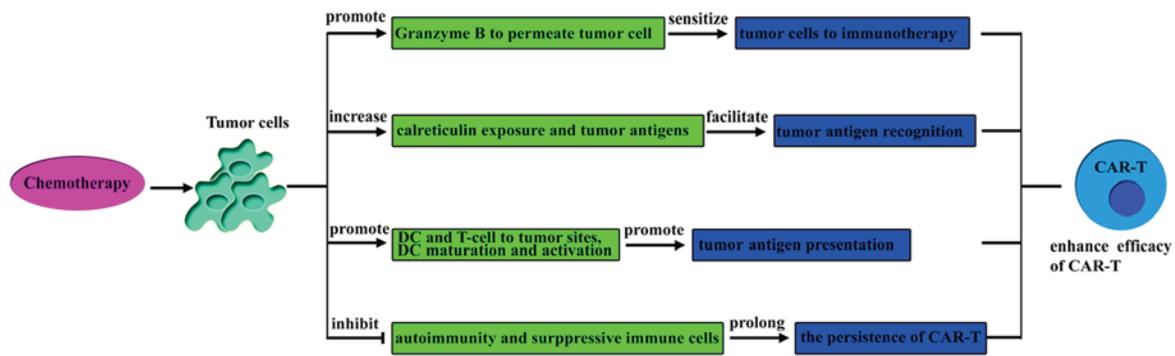


Figure 2. Mechanisms for how chemotherapy improves the efficacy of CAR-T. CAR-T, chimeric antigen receptor T-cell; DC, dendritic cells.

low-dose chemotherapeutics were not detrimental to adoptive T cells (40-42).

Chemotherapy is able to inhibit autoimmunity and prolong the persistence of CAR-T cells in vivo. Accumulating preclinical and clinical studies have demonstrated that after repeated cycles of intensive treatment with chemotherapy, autoimmunity is inhibited, which is a lethal side effect (43-45). Nevertheless, inhibited autoimmunity may increase the efficacy of adoptive T-cell transfer in cancer patients (19). Early CAR-T cell therapy trials without conditioning chemotherapy demonstrated a short persistence of CAR-T cells and poor results in the treatment of solid tumors (15,16,46). Recent studies have confirmed that conditioning chemotherapy is able to inhibit autoimmunity and remove suppressive cells to prolong the persistence of CAR-T cells *in vivo*, thereby boosting their curative effects (47,48). In addition, the studies demonstrated that conditioning chemotherapy is able to counteract the potential immunogenicity of CAR-T cells and provide homeostatic cytokines to CAR-T cells to reduce the toxicity (47,48).

T-cells can amplify the efficacy of chemotherapy. It has been demonstrated that the innate and adaptive immune systems are able to contribute considerably to the efficacy of chemotherapy in the treatment of cancer (49). A recent study by Wang *et al* (50) in Cell indicated that effector T-cells abrogate stroma-mediated chemoresistance in ovarian cancer. Wang *et al* (50) demonstrated that fibroblasts release glutathione and cysteine, which contribute to chemoresistance. T-cells were able to change the metabolism of glutathione and cysteine by releasing IFN- γ in fibroblasts via the Janus kinase 1/signal transducer and activator of transcription 1 signaling pathway, thereby abolishing chemoresistance. In addition, accumulating preclinical and clinical studies have demonstrated that following repeated cycles of intensive treatment with chemotherapy, autoimmunity was inhibited, which is a lethal side effect (43-45). Therefore, it is urgent to evaluate the application of adoptive T cells to restore the human immune system and to maintain the stability of the internal environment. Therefore, as one example of adoptive T-cells, CAR-T cells can amplify the efficacy of chemotherapy.

In conclusion, the combination of chemotherapy with CAR-T cell therapy may have synergistic effects, and further research on novel combination strategies may provide an opportunity to use the full potential of CAR-T cells in the treatment of solid tumors.

4. Feasibility of using CAR-T cells with radiotherapy for treatment of solid tumors

Currently, accumulating evidence supports the concept that antitumor effects can be additive or even synergistic when radiotherapy is combined with immunotherapy (51,52). There are a number of rationales for employing CAR-T cells in conjunction with radiotherapy when treating solid tumors.

Radiotherapy is able to improve the efficacy of CAR-T cells. It has been increasingly observed that apart from eradication of tumor cells, radiotherapy can also stimulate tumor-specific immunity to enhance tumor control both locally and distantly (34,53). This observation may serve as a rationale to demonstrate that radiotherapy can improve the efficacy of CAR-T cells in the treatment of solid tumors (Fig. 3).

Radiotherapy is able to sensitize tumor cells to tumor-specific cytotoxic lymphocytes. Reports have demonstrated that the local radiation of tumors can enhance the expression of MHC class I molecules and tumor-specific antigens on irradiated tumor cells, rendering them more susceptible to tumor-specific cytotoxic lymphocytes, which boosts the efficacy of adoptive CTL immunotherapy (51,53,54).

Radiotherapy is able to create a tumor microenvironment conducive to CAR-T cell trafficking and infiltration. It has been generally accepted that the trafficking and infiltration of effector T cells into solid tumors is required for successful antitumor immune responses (55). Studies have indicated that following radiation, the release of IFN- γ and DAMPs increases, which attracts immune effector cells to the tumor microenvironment, boosting the trafficking capability of immune effector cells and creating a tumor microenvironment conducive to T-cell infiltration (56-58). Consistent with this finding, it has been proposed that local radiation may induce the expression of certain chemokines, including C-X-C motif chemokine ligand (CXCL)9, 10 and 16, to promote the recruitment of T-cells into the tumor microenvironment and to increase the infiltration of immune effector cells (56,59,60). Additionally, local radiation also contributed to a greater infiltration of lymphocytes into the tumor as it reverses the non-adhesive phenotype of the tumor endothelium (57).

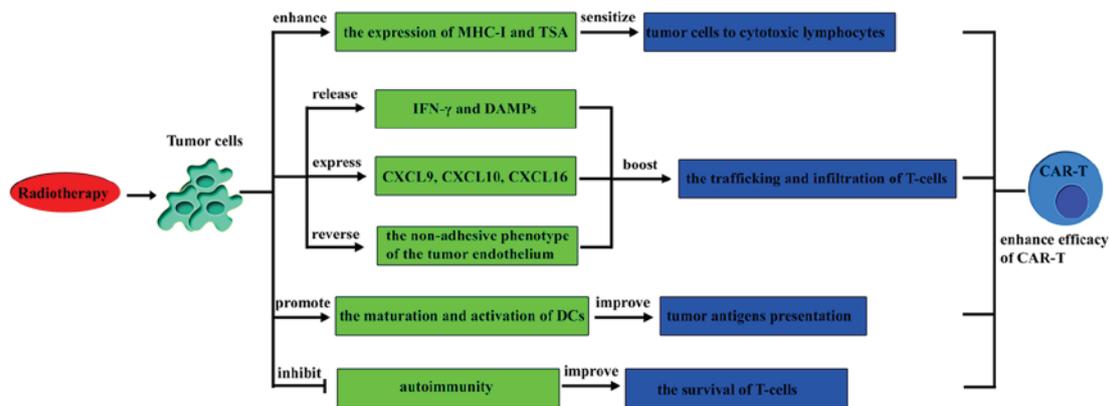


Figure 3. Mechanisms for how radiotherapy improves the efficacy of CAR-T. DC, dendritic cells; TSA, tumor specific antigen; CAR-T, chimeric antigen receptor T-cell; CXCL, chemokine C-X-C motif ligand; DAMP, damage-associated molecular pattern, IFN, interferon; MHC-I, major histocompatibility complex 1.

Radiotherapy is able to improve tumor antigen presentation. It has been increasingly observed that radiotherapy is able to increase tumor antigen presentation (61). Radiotherapy is able to induce apoptosis and necrosis of tumor cells, causing them to release danger signals, including HMGB1 (34). Subsequently, the danger signals and tumor antigens may potentially trigger type I IFN in the tumor microenvironment, serving as a link between innate responses and adaptive immunity (62,63). This interaction between the innate responses and adaptive immunity has critical roles in promoting the maturation and activation of DCs to improve tumor antigen presentation (64-66).

Rationale behind T-cells amplifying the efficacy of radiotherapy. It has been proposed that radiotherapy is often associated with local or distal tumor relapse, and the response to radiotherapy is partially dependent on the tumor microenvironment and the local immune system, particularly the T-cells (56). Studies have indicated that CD8⁺ T-cells and their cytokines have an essential role in maintaining control over irradiated solid tumors to reduce recurrence and metastasis (55,67,68).

Furthermore, following local radiation therapy, CTL may not only be attracted to irradiated tissue to induce local responses but may also be able to inhibit distant tumors, which is a phenomenon known as the abscopal effect (69). This changes radiotherapy from a regional antitumor therapeutic modality to a therapy that can target distant metastasis. Furthermore, CAR-T cell therapy can enhance the functions of T-cells, so the antitumor effects should be further amplified by combining radiotherapy with CAR-T cell therapy (70). Clinical trials evaluating the feasibility of this approach are starting. For instance, a phase I study at Duke University (ClinicalTrials.gov identifier, NCT02664363) aims to evaluate the safety and efficacy of EGFRvIII CAR-T cells in combination with the standard of care radiation therapy. Based on the rationale above, the present authors hypothesize that a combination of CAR-T cell therapy and radiotherapy for treatment of solid tumors should be additive or synergistic and may add a new perspective to existing treatments.

5. Feasibility of employing CAR-T cell therapy with chemoradiotherapy for treatment of solid tumors

Chemoradiation therapy (CRT) has an important role in the treatment of solid tumors. However, Yovino and Grossman (71)

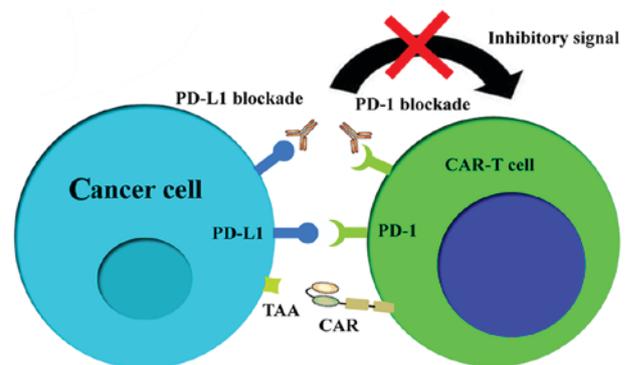


Figure 4. Mechanism of action of CAR-T with PD-1/PD-L1 blockade. PD-1, programmed death-1; PD-L1, programmed death-1 ligand; TAA, tumor associated antigen; CAR, chimeric antigen receptor.

indicated that CRT is able to result in treatment-associated toxicities, including effects on host immunity, such as lymphopenia. In addition, a number of studies have demonstrated T cells would be exhausted when solid tumors are treated with CRT, which result in elimination of a subset of immune cells (72,73). This might reduce the antitumor functions of CRT and promote tumor metastasis and recurrence (74,75). In particular, T cells are critical in mediating cellular immunity against neoplastic cells (76-78). Therefore, it might be feasible to infuse adoptive T cells in order to improve the antitumor effect of chemoradiotherapy and to prevent metastasis and recurrence. Unfortunately, given that the development of CAR-T cell therapy in solid tumors is at early stages, studies that combine chemoradiotherapy and CAR-T cell therapy have not yet been completed.

Several studies have demonstrated that the immune system has a critical role in promoting antitumor defense, and a low absolute lymphocyte count during therapy is associated with poorer clinical outcomes (79-81). Although the role of CAR-T cell therapy in combination with CRT in solid tumors is unknown, the approach remains promising. Buka *et al* (82) indicated that combining CRT with CAR-T cell therapy may be particularly efficacious due to the increased density of T cells following CRT that is associated with a median survival rate 2.5 times longer than the CRT monotherapy. Meanwhile, Zitvogel *et al* (83) and Aranda *et al* (84) indicated that CRT

might promote the antitumor efficacy of CAR-T cell therapy as a number of CRT regimens can stimulate T cells, which accounts for the clinical response induced by these therapies.

6. Feasibility of CAR-T cell therapy with other immunotherapy strategies for treatment of solid tumors

Accumulating evidence has demonstrated that the immunosuppressive microenvironment induced by solid tumors can limit the efficacy of CAR-T cell therapy (85). Tumors can evade immune surveillance by stimulating immune inhibitory receptors on T cells, including T-cell membrane protein-3, cytotoxic T lymphocyte-associated antigen (CTLA)-4 and programmed death (PD)-1 (86-88). The majority of solid tumors upregulate immune checkpoint ligands, leading to the inhibition of CAR-T cell therapies by stimulating immune inhibitory receptors (89,90). Antibodies that block CTLA-4 (ipilimumab and tremelimumab), PD-1 (nivolumab, pembrolizumab and pidilizumab) and PD-L1 (MDX-1105 and MPDL3280A) have recently been approved by the US Food and Drug Administration for use in certain solid tumors (91). Considering this issue, whether greater curative effects are obtained after combining CAR-T cell therapy with immune checkpoint inhibitors were examined.

Preclinical studies by John *et al* (92), Liu *et al* (93) and Cogdill *et al* (94) have demonstrated that CAR-T cell therapy and PD-1 blockade was highly synergistic, leading to long-term survival without causing any signs of pathology *in vivo*. Similar effects have been observed by Moon *et al* (95), Burga *et al* (96), Suarez *et al* (97) and Rosewall Shaw *et al* (98). The proposed mechanism of action of CAR-T with PD-1/PD-L1 blockade is illustrated in Fig. 4. To overcome the immunosuppressive microenvironment, Li *et al* (99) engineered T cells to secrete checkpoint inhibitors that target PD-1 (CAR. α PD1-T) and evaluated its efficacy in a human lung carcinoma xenograft mouse model. Li *et al* (99) demonstrated that the secretion of anti-PD-1 enhanced the antitumor activity of CAR-T cells and prolonged overall survival. Furthermore, Serganova *et al* (100) showed that employing prostate-specific membrane antigen-specific CAR-T cell therapy alone to treat prostate cancer was unsuccessful, whereas the combination of CAR-T cell therapy and a PD-1 blockade provided a partial, short-duration and sub-optimal response (100).

In clinical trials, the combination of CAR-T cell therapy and PD-1 blockade has been further evaluated. Gargett *et al* (101) revealed that combining a PD-1 checkpoint inhibitor with CAR-T cell therapy may be useful in augmenting the efficacy and persistence of CAR-T cells in patients.

A primary reason for the limited application of CAR-T cell therapy in solid tumors is that penetration by immune cells is difficult (102). It has been confirmed that CAR-T cell therapy could be directed to the tumor tissues through the coexpression of chemokine receptors (CXCR2 or CCR4) or through combination with chemokines (103,104). Xia *et al* (105) suggested that combining an oncolytic virus with CAR-T cell therapy may be particularly efficacious in stimulator of interferon genes protein-inactivated and type I IFN-disrupted tumors. By contrast, Ajina and Maher (106), Kim (107) and Scott *et al* (108) indicated that oncolytic virus infection might augment entry and mobilization of CAR-T cells, and mitigate

or reverse local immunosuppression and enhance the function and persistence of CAR-T cell effectors.

With regards to efficient targeting of CAR T-cells, Nishio *et al* (109) combined GD2-specific CAR-T cell therapy with an oncolytic virus expressing RANTES and IL-15 in the treatment of neuroblastoma-bearing mice. They demonstrated that RANTES and IL-15 attracted CAR-T cells and promoted their local survival. In addition, the survival of CAR-T cells in solid tumors was improved by combining CAR-T cells with the armed oncolytic virus (110).

7. Conclusion and discussion

CAR-T cell therapy has an important role in controlling and eradicating malignant cells, particularly in the treatment of hematologic malignancies. However, expanding the use of CAR-T cell therapy to solid cancers raises challenges (111). When summarizing the relevant studies, it was found that combination therapy based on CAR-T cell therapy for solid tumors is feasible and may allow the full potential of CAR-T cell therapy to be realized.

However, it is critical to determine which patients require combination strategies, what combinations are best in any given patient and how best to combine such agents. First, some patients that benefit from monotherapy do not require combination therapy and should not be administered combination therapy in order to avoid toxicities associated with combination therapy. Therefore, it is urgent for us to develop biomarkers to identify such patients to preselect them for monotherapy (112). Secondly, for patients who require combination therapy, the identification of such predictive biomarkers is also important to determine the optimal combination of therapies. Thirdly, to employ novel combination therapy strategies (a mixture of CAR-T cell therapy and chemotherapy, radiotherapy, chemoradiotherapy or other regimens) in preclinical and clinical settings, the timing, dosage, frequency, fractionation, and treatment sequences need to be defined.

In conclusion, novel combination strategies for the treatment of solid tumors deserve further study to minimize toxicity while maximizing antitumor efficacy.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

LZC contributed the central idea and analysed most of the data. JJX analyzed and interpreted the data regarding the combination of CAR-T with chemotherapy in the treatment of solid tumors. YLW analyzed and interpreted the data

regarding CAR-T monotherapy in solid tumors treatment. JS analyzed and interpreted the data regarding the combination of CAR-T with radiotherapy in the treatment of solid tumors. JL and QGL analyzed and interpreted the data regarding the combination of CAR-T with other immunotherapy strategies in the treatment of solid tumors. JJX and YLW wrote the initial draft of the paper. The remaining authors finalized this paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interest.

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