

Chimeric antigen receptor T cell therapy in cancer: Advances and challenges

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Abstract

Chimeric antigen receptor (CAR) T-cell therapy has drawn the most attention ever in the treatment of hematologic malignancies due to its impressive efficacy in heavily pretreated patients. However, the use of CAR T-cell therapy has just started in the field of solid tumor. Till now, four CAR T-cell therapies have been approved in the world, and an increasing number of patients will receive this expensive treatment. Thus, we will briefly talk about the advances and challenges in the adventure of CAR T-cell therapy.

Keywords: CAR T-cell, solid tumor, cancer

Chimeric antigen receptor (CAR) T-cell therapy is novel tumor immunotherapy and its advent is a huge breakthrough in adoptive cell therapy. CAR T-cells are genetically developed based on primary T-cell engineering and the use of artificial synthetic receptors which enable T-cells with high affinity for tumor antigens to recognize specific antigens on tumor cells independent of major histocompatibility complex (MHC), rousing the silencing T-cells to exert a persistent anti-tumor effect. This feature could effectively prevent tumor cells from down-regulating the expression of MHC leading to immune evasion. At present, CAR T-cell has developed to the fourth generation, and different generations of CARs differ in the aspects of T-cell activating domains, the co-stimulatory signal domain (CD28 or 4-1BB) and the additional different cytokine transgene. CAR T-cell therapies have widely shifted the worrisome situation of relapsed/refractory (R/R) hematological malignancies. However, the response observed in solid tumors tends to be less robust and effective. Therefore, multitudinous clinical trials of the safety and efficacy of CAR T-cell therapy directed at various types of cancers are in process.

CAR T-cell therapies have achieved unprecedented success in hematologic cancers, including diffuse large B-cell lymphoma (DLBCL), primary mediastinal B-cell lymphoma (PMBCL), high-grade B-cell lymphoma (HGBL),

acute lymphoblastic leukemia (ALL), chronic lymphocytic leukemia (CLL), and multiple myeloma (MM), etc. In phase 2 global study for patients with R/R B-cell ALL, the efficacy of Tisagenlecleucel (Kymriah) therapy was satisfactory where the overall response rate (ORR) within 3 months was as high as 81%. The rates of event-free survival (EFS) and overall survival (OS) at 12 months were 50% and 76% respectively [1]. In refractory large B-cell lymphoma (LBCL), patients with Axicabtagene Ciloleucel (Yescarta) treatment, which the objective response could attain 83%, while the complete response rate (CRR) up to 58%. In addition, the median OS was not reached during a 2-year follow-up [2]. These exciting clinical results prompted the FDA to accelerate the approval of Yescarta and Kymriah as indications for CD19+ R/R ALL/ LBCL in 2017. A new study about the first-line application of CAR T-cell therapy (Yescarta) in LBCL has suggested significant efficacy and controlled security, with 92% ORR and 75% CRR. In addition to CARs targeting CD19, the ongoing clinical trials include CD20 targeting, CD22 targeting, CD19/CD20 dual specific targeting as well as CD19/CD22 for B-cell hematological malignancies. Moreover, there are also several targets such as CD30, CD5, CD7 focused on the aggressive T-cell malignancies. The CD30+ CAR T-cells used in R/R HL patients have achieved gratifying results, with an ORR of 72% [3]. The results of the series of studies indicate that CAR T-cell therapy will occupy an important position in the field of hematological tumors in the future.

CAR T-cell therapies have also been remarkably expanded in clinical trials of solid tumors, such as brain tumor, liver cancer, pancreatic cancer, breast cancer, ovarian tumor, and colorectal cancer, etc. Nevertheless, relevant data re-

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Received: 12 August 2021 / Accepted: 19 August 2021

flecting clinical efficacy are unfavorable. A meta-analysis of 262 patients showed that the overall pooled response rate of CAR T-cell therapies in solid tumors was 9% [4]. In neuroblastoma, 3 of 18 patients had a CR with GD2-CAR T-cells infusion and the CAR-cells persisted for 6 weeks [5]. In a phase I study of glioblastoma, 18 patients with R/R were treated with anti-EGFRvIII CAR T-cells, but the objective response was not seen and the CAR cell's persistence time was related to the dose of infusion cells [6]. Feng *et al.* studied the efficacy and safety of CAR T-cells targeting HER2 in 18 patients with advanced biliary tract cancers and pancreatic cancers, 1 obtained partial response (PR) and 5 achieved stable disease (SD). Furthermore, the median progression-free survival (PFS) was 4.8 months [7]. We could observe that the response of CAR T-cell therapy in solid tumors appears to be far less effective than that of hematological tumors. This problematic status quo is bound by several factors, including the scarcity of ideal tumor-specific antigens (TSA), high tumor heterogeneity, and a hostile tumor microenvironment (TME). Many strategies and approaches have been tried to overcome these existing challenges. For example, CAR T-cell could recognize antigens expressed in non-malignant tissues causing fatal consequences, so the multi-target CAR T-cell were designed to ensure the specificity of target antigens and reduce CAR T-cells binding to normal tissues. There are many barrier tissues around the tumor and a lack of chemokine, which makes it difficult for CAR T-cell to infiltrate into the tumor. Studies have shown that local or intratumoral injection of CAR T-cells could exert a strong and continuous anti-tumor effect at tumor sites, and also reduce the risk of systemic toxicities caused by off-target. Immune checkpoints are highly upregulated in the microenvironment of solid tumors and seriously affect the proliferation and function of T-cell. As a result, agents enable to enhance T-cell function, such as immune checkpoint inhibitors, IL-2, or IL-12, may be combined with CAR T-cell therapy, to improve the undesirable efficacy. As a broad array of CAR T-cell therapies become increasingly used, recognition and understanding of their unique toxicities are of the utmost importance. Cytokine release syndrome (CRS) and neurotoxicity are the most major and severe clinical toxicities after CAR T-cells infusion, which are induced by T-cell engagement and activation [8]. There are still many unknowns about the mechanism leading to these adverse events. A recent study found that targeting cytokines, such as granulocyte-macrophage colony-stimulating factor, are believed to be effective for neurotoxicity and CRS without compromising efficacy. The current pressing issue is to formulate a consensus guideline of the management of these immune-related toxicities for clinical physicians. Looking forward to the future, great efforts are still needed in the innovative design

of CARs, the identification of new tumor targets, the rational combination with other therapies, and new methods to improve the efficacy and safety of CAR T-cell therapy. Only when we better understand the pros and cons of this revolutionary treatment can we better apply it to the clinic and benefit patients.

Declaration

Financial support and sponsorship: None.

Conflict of interest: Liang Wang is a member of the Editorial Board of *Aging Pathobiology and Therapeutics*. All authors declare no conflict of interest and were not involved in the journal's review or decisions related to this manuscript.

Ethical approval and consent to participate: Not applicable.

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Cite this article as: Liang Y Z, Liang W. Chimeric antigen receptor T cell therapy in cancer: Advances and challenges[J]. *Aging Pathobiology and Therapeutics*, 2021, 3(3): 46-47.