The newest medicine: Chimeric antigen receptor T-Cell immunotherapy (CAR-T).

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Abstract

Recent approval of chimeric antigen receptor T-cell immunotherapy (CAR-T) for the clinical use represents a significant progress in the human defense war against cancer, and validates a novel bio-pharmaceutical platform that synergizes the strengths of adoptive cellular immunotherapy as well as molecular genetic engineering. With the curable efficacy for refractory B-cell malignancy, CAR-T is increasingly contributing to a paradigm shift toward immunotherapy in oncologic medicine and pharmaceutical innovation. Through optimization of the relevant bio-technological aspects with timely translation from science to medicine, CAR-T pipeline is expected to go beyond hematological application, to deliver additional therapeutic benefits to the patients with solid tumors.

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Introduction

On August 30, 2017, Food and Drug Administration (FDA) of USA approved the first chimeric antigen receptor T-cell immunotherapy (CAR-T) to treat refractory or relapsed acute B cell leukemia, which declares that a novel curable medicine is officially available for the patients in need [1]. To date, CAR-T represents the highest achievement of immune gene/cell-based therapeutic innovation through a long-term struggling effort. Impressively in recent years, CAR-T along with immune checkpoint inhibitors is transforming the landscape of oncologic medicine and pharmaceutical industry [2,3].

Inspired by clinical and pathological observations, the idea of biological therapy against tumors taking the advantages of cellular and molecular approaches to augment immune surveillance was initially proposed decades ago. However, immune cell modulation-based strategies have historically remained out of the mainstream treatment in clinical oncology due to their disappointing or marginal therapeutic efficacy until recently [2,4]. As a hallmark of immunotherapeutic renaissance in contemporary oncology, the success of CAR-T is largely attributed to several key aspects of scientific progress, including identification of tumor-associated antigens, delineation of specific immune response, biological dissection of T-cell receptor (TCR) and monoclonal antibody (mAb) [1,5,6].

In principal, CAR-T protocol starts with isolation of T-lymphocytes from a cancer patient. Subsequently, a chimeric molecule of TCR and mAb variable chain is inserted into the autologous T lymphocytes by genetic engineering, which thus can recognize the tumor antigen without major histocompatibility complex (MHC) restriction, and be activated to kill malignant cells selectively [2,6]. Following ex vivo expanding over several billions, CAR-T cells are then re-infused back into the patient, who should thereby be subjected to careful monitoring [4,6]. In recent decade, CAR-T cells targeting more than a dozen of tumor antigens have been investigated for therapeutic effectiveness against various neoplasms through a number of well-designed clinical studies, in which cluster of differentiation19 (CD19) in B-cell malignancies appears to be the most attractive tumor antigen targeted by this approach [1,6]. As a popularly known story of clinical success, the first pediatric patient named Emily Whitehead with pre-B acute lymphoblastic leukemia that had failed standard chemotherapy and was then shifted on CD-19-targeted CAR-T- experimental treatment in 2012. Excitingly weeks following this procedure, a complete response was achieved. Now more than five years later, she is still in remission, and going to school like other normal children (www/chop.edu/stories/relapsed-leukemia-Emily-story). Overall, CD19-re-directed CAR-T cells were able to confer complete remission (CR) rate ranging from 70% to 90% in the clinical trials for the patients with drug-resistant or relapsed acute lymphoblastic leukemia [2,6]. In addition, CD19-CAR-T cells have also been revealed to exert a response rate of 57% for the patients with end-stage advanced chronic lymphocytic leukemia, of which more impressively some cases remained CR without relapse for over 4 years [2,7].

While CAR-T cell-based medicine has achieved a significant success in managing one group of hematological malignancies including lymphocytic leukemia, lymphoma and multiple myeloma, most clinical trials with this approach to treat solid tumors were disappointing without clear therapeutic efficacy. Several pathological hurdles of solid neoplasm may account for the problem, such as T cell trafficking obstacles and immunosuppressive microenvironment [8,9]. In this regard, it has been proposed to circumvent the challenges arising from the perspective of solid tumors through arming CAR-T cells with expression of pro-migration chemokine receptors and combining application with checkpoint inhibitor blockade, respectively [3,8,10]. On the other hand, the clinical adverse events resulting from CAR-T therapy have been noticed, but luckily they are usually manageable or reversible. Ideally, collateral organ damage due to on-target off-tumor toxicity can be prevented by selecting highly specific tumor antigens that do not express in normal tissues at all [2]. Realistically, CD19 as a tumor-associated antigen is simultaneously expressed in both neoplastic and normal B- cells, explaining CD19 CAR-T

cells-induced B-cell aplasia which needs immunoglobulin replacement and long-term follow-up accordingly [6]. Besides this issue, while cytokine release syndrome can be mitigated with the interleukine-6-blocking antibody, neurologic toxicities, without known mechanisms yet, are self-limited over several days in most patients [6,11].

As a highlighted translational success from the interdisciplinary scientific research and industrial development, the approval of CAR-T medicine has validated a clinical utility of the emerging comprehensive bio-pharmaceutical platform that combines adoptive cellular immunotherapy and molecular genetic engineering [1,6]. With the unique high efficacy in fighting refractory B-lymphocytic malignancy, CAR-T strategy is substantially contributing to the rise of immunotherapy as an advanced milestone following chemotherapy and targeted medicine in mainstream oncologic treatments [2]. Currently, there are hundreds of ongoing clinical trials using CAR-T approach to target numerous antigens, such as CD20 and CD33 among others, in a wide spectrum of tumor types, which will hopefully deliver expanded therapeutic benefits to more patients, in particular to those with hematological malignancies [11,12]. Optimally, it is anticipated that coming waves of CAR-T portfolio can go beyond traditional medicine to further improve clinical outcomes in the cases of solid neoplasms, upon discovery of more tumor-specific antigens and more efficacious managing options of tumor microenvironment in the era of precision/individualized medicine [2,8].

References

1. Sheridan C. First approval in sight for Novartis' CAR-T therapy after panel vote. Nat Biotechnol. 2017;35:691-3.
2. Chen D, Zhang X. Cellular immunity augmentation in mainstream oncologic therapy.Cancer Biol Med. 2017; 14:121-8.
3. Pennock GK, Chow LQ. The evolving role of immune checkpoint inhibitors in cancer treatment.Oncologist 2015;20:812-22.
4. Miller JF, Sadelain M. The journey from discoveries in fundamental immunology to cancer immunotherapy. Cancer Cell. 2015;27:439-49.
5. Chen D, Lee F, Cebra JJ, et al. Predominant T-cell receptor Vbeta usage of intraepithelial lymphocytes during the immune response to enteric reovirus infection. J Virol. 1997;71:3431-6.
6. Almåsbak H, Aarvak T, Vemuri MC. CAR T cell therapy: A game changer in cancer treatment. J Immunol Res. 2016;2016:5474602.
7. Porter DL, Hwang WT, Frey NV, et al. Chimeric antigen receptor T cells persist and induce sustained remissions in relapsed refractory chronic lymphocytic leukemia. Sci Transl Med. 2015;7:303ra139.
8. Zhang H, Ye ZL, Yuan ZG, et al. New Strategies for the Treatment of Solid Tumors with CAR-T Cells. Int J Biol Sci. 2016;12:718-29.
9. Chen D, Zhang X. Tipping tumor microenvironment against drug resistance. Oncol Trans Res. 2015;1:1.
10. Liu X, Ranganathan R, Jiang S, et al. A chimeric switch receptor targeting pd1 augments the efficacy of second generation CAR T cells in advanced solid tumors. Cancer Res. 2016;76:1578-90.
11. Dai H, Wang Y, Lu X, et al. Chimeric antigen receptors modified T-cells for cancer therapy. J Natl Cancer Inst. 2016;108:djv439.
12. Chmielewski M, Hombach AA, Abken H. Antigen-Specific T-Cell Activation Independently of the MHC: Chimeric Antigen Receptor-Redirected T Cells. Front Immunol. 2013;4:371.

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