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Application of CAR-T Cell Therapy in Multiple Myeloma

Zhenchun Wu

College of animal medicine, Shanxi Agricultural University, Jinzhong City, Shanxi Province, 030600, China

Abstract

Multiple myeloma is a malignant tumor of the blood system in which B lymphocytes in bone marrow differentiate into dysplastic plasma cells. It accounts for about 13% of hematological malignancies and it is common in people aged 60-70. Clinically, it is often manifested as bone pain, anemia, and amyloidosis in the tongue, heart and other parts.In recent years, with the continuous progress of new drugs and medical technology, MM has made a great breakthrough in the treatment. Chimeric antigen receptor-T cell therapy (CAR-T) in the last five years has received extensive attention, and has achieved remarkable effects in B-cell lymphoma and acute lymphoblastic leukemia. This article focuses on the target of CAR-T cell therapy for multiple myeloma, the side effects and prospects.

Keywords

Chimeric Antigen Receptor of T-cell Therapy (CAR-T); Multiple Myeloma (MM); CD19; CD38; BCMA.

1. Introduction

Multiple myeloma (MM) is a hematological cancer in which normal plasma cells in the blood differentiate into malignant cancer cells [1]. Clinically, it is often manifested as bone pain, anemia, renal function damage, and amyloidosis in the tongue, heart and other parts. Multiple myeloma accounts for more than 1% of the world's annual incidence rate. It is estimated that the number of new cases of multiple myeloma in Germany is about 6000,[1] About 28850 new multiple myeloma cases were diagnosed in the U.S in 2015. [2] The actual event rate of MM in China is not exact yet, but the overall trend is increasing. [3] At present, there is no specific drug for multiple myeloma in clinic. New drugs such as proteasome inhibitors, immunomodulators and surgery, chemotherapy and other technologies can only inhibit the growth of tumor cells, but they can't completely kill tumor cells. After the treatment, it is found that the recurrence rate and mortality rate of the disease are very high. [4] CAR-T Cell products for children with acute lymphoblastic leukemia and adult diffuse large B-cell lymphoma subtype has good curative effect, and it has been approved for US FDA clinical use. Therefore, in view of this situation, CAR-T cell therapy also has broad prospects of MM therapy. In this paper, CD19, CD38 and BCMA are introduced.

2. CAR-T Cell Therapy for Multiple Myeloma

Multiple myeloma (MM) is recognized as the second largest hematological malignancy in the world. The local microenvironment of bone marrow can provide good survival and proliferation conditions for tumor cells, which can protect multiple myeloma cells from drug-induced apoptosis. [5] In view of this situation, CAR-T cell therapy has become the only choice. CAR-T cell therapy through the specific modification of part of the gene sequence allows CAR to specifically affect the antigen of tumor cells. After the antigen binds to the receptor, T cells are activated to kill tumor cells. [7] This cell therapy can not only avoid the immune tolerance

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of drugs, but also use chimeric antigen receptor to specifically recognize tumor associated antigens, so as to exert the powerful killing ability of T cells. Moreover, the fourth generation of CAR-T cell therapy can overcome the inhibition of tumor microenvironment on CAR-T cells, which is a great progress in CAR-T cell therapy. [6] However, no perfect antigen has been found to specifically recognize tumors without damaging normal tissues. [7] The following will list the new antigens that have been found and used in clinical research.

2.1. CAR-T Cell Therapy Targeting CD19

CD 19 is not only specifically expressed in the process of normal B cell differentiation, but also expressed in B-cell-derived malignant tumors. [8] At present, the US Food and Drug Administration (FDA) has approved the treatment of CAR-T for CD19, which has obviously efficacy in the treatment of adult acute lymphoblastic leukemia and diffuse large B-cell lymphoma. Because MM is a hematological malignancy with abnormal differentiation of B lymphocytes in bone marrow, MM can also express CD19, therefore, MM treatment may use CD19 as a target. Studies have shown that human trials targeting CAR-T cells of CD19 or BCMA in MM have achieved early success. Although the expression of CD19 in MM was very low, in a clinical trial of Garfall, patients received CD19-CAR-T after autologous stem cell transplantation (ASCT). Only 2 patients (2 / 10) had prolonged PFS(progression-free survival). After that, CTL019 could not be detected in the blood and bone marrow of patients, which indicated that the activity of CD19-CAR might decrease with the treatment time. [9]

In addition, the First Affiliated Hospital of Suzhou University (NCT03455972)prescribed to test for specific CD19 / BCMA after ASCT Machine efficiency. [10] The therapeutic effect of cell therapy targeting CD19 alone is limited in clinic, so it is necessary to carry out double target therapy or find other targets.

2.2. CAR-T Cell Therapy Targeting CD38

Sanofi announced on April 20, 2021 that the European Commission has approved sarclisa combined with carfilzomib, kypolis ® and KD, a drug targeting CD38. The sarclisa + KD protocol was approved by FDA in March 2021. CD38 was expressed in primary tumor cells and malignant plasma cell tumor cells, [11] However, CD38 was rare in normal lymphocytes and bone marrow cells.[10] The CD38-focused CAR-T cell therapy target offers new ideas for the treatment of MM. Daratumumab was approved by FDA in 2015 for the treatment of mm, and experiments show that the combination of daratumumab and immunomodulators can improve the effect of daratumumab. [12-13] However, CD38 CAR-T can attack the body tissues and cause autoimmune diseases. Therefore, it is necessary to continue to improve the CD38-CAR-T cell therapy to reduce its toxic response. [7]

2.3. CAR-T Cell Therapy Targeting BCMA

On December 8, 2020, Keji biological announced that its CT053 human anti BCMA auto CAR-T cell injection passed the CDE publicity period, and was included in the "breakthrough drug variety", and the proposed indication was RRMM.[14] NCI published the results of treating MM with CAR-T cells on ASH in 2017. The results showed that BCMA-CAR-T cells could indeed kill MM cells. [15] Hematology center of Jiangsu People's Hospital analyzed the data of two RRMM patients who had conducted phase 1 clinical trial and one patient who had enrolled in LCAR-B38M phase 2 clinical trial. CTX regimen (cyclophosphamide 300mg / m2×3d) was used 5 days before CAR-T cell therapy, and the latter used FC regimen (cyclophosphamide 250 mg / m2×3d, Fludarabine 25mg / m2 × 3d）. The results showed that the effect of BCMA targeted CAR-T cell therapy on elderly patients was not different from that of young patients. [16] It can be concluded that BCMA can be an ideal target for the treatment of MM.

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3. Prospect of CAR-T Cell Therapy in Multiple Myeloma

CAR-T cell therapy can induce Cytokine Release Syndrome (CRS), Immune Cell Associated Neurotoxicity Syndrome (ICANS) and other pathological changes. Although CAR-T cell therapy has a good effect on the treatment of myeloma, it is only suitable for patients with Relapsed and Refractory Multiple Myeloma (RRMM). To achieve the effective treatment of MM with CAR-T cell therapy,it is the most important to find the key that can detect strong expression in MM tumor cells and can't be expressed in normal cells, especially in important organ cells. [17] Although CAR-T cell therapy has made a successful breakthrough in the treatment of malignant hematological diseases,the effect of treating solid tumors is limited. [18] Therefore,CAR-T cell therapy has great prospects for treating multiple myeloma, but the task is also very arduous.

References

[1] Gerecke C, Fuhrmann S, Strifler S, Schmidt-Hieber M, Einsele H, Knop S. The Diagnosis and Treatment of Multiple Myeloma. Dtsch Arztebl Int. 2016 Jul 11;113(27-28):470-6. doi: 10.3238/arztebl.2016.0470. PMID: 27476706; PMCID: PMC4973001.

[2] Michels TC, Petersen KE. Multiple Myeloma: Diagnosis and Treatment. Am Fam Physician. 2017 Mar 15;95(6):373-383. PMID: 28318212.

[3] Chinese Hematology Branch of Chinese Medical Doctors Associa- tion， Hematology Branch of Chinese Medical Association， Multiple Myeloma Professional Committee of Chinese Medical Doctors Asso-ciation. Chinese multiple myeloma diagnosis and treatment guide- lines (revised in 2017)[J]. Chinese Journal of Internal Medicine,2017,56(11):866-870.

[4] Cornell RF，Kassim AA. Evolving paradigms in the treatment of re- lapsed /refractory multiple myeloma: Increased options and in- creased complexity［J］. Bone Marrow Transplant，2016，51(4):479－491.

[5] Shay G,Hazlehurst L,Lynch CC,et al.Dissecting the multiple myeloma-bone microenvironment reveals new therapeutic opportunities[J].Journal of Molecular Medicine, 2016,94(1):21-35

[6] Development and Application of Chimeric Antigen Receptor T Cells in the Treatment of Hematological Tumors [J],Journal of Third Military Medical University,2019,41(23):2261-2266.

[7] Li Yihao, Wang Jianxun. Advances in the Treatment of Multiple Myeloma by CAR-T Cells[J]. Journal of Modern Oncology, 2019, 027(020):3729-3732.

[8] Liu Jiahui, An Gang, Wang Jianxiang. Advances of CAR-T Cell Therapy in Multiple Myeloma [J]. Journal of Clinical Hematology, 2019,032(07):494-498

[9] Garfall AL, Stadtmauer EA, Hwang WT, et al.Anti-CD19 CAR T cells with high-dose melphalan and autologous stem cell transplantation for refractory multiple myeloma[J].JCI Insight,2018,3(8):e 120505

[10] Chang Xiangxiang, Wei Zhongling, Zheng Xingyuan, etc. Treatment Progress of Multiple Myeloma [J]. Chinese Journal of Clinical Pharmacology and Therapeutics, 2020,25(1):107-116

[11] Harada,Kawano MM,Huang N,et al.Phenotypic difference of normal plasma cells from mature myeloma cells[J] .Blood,1993,81(10):2658-2663.

[12] Palumbo A, Chanan-Khan A, Weisel K,et al.Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma[J].N Engl J Med. 2016 Aug 25;375(8):754-766.

[13] imopoulos MA, Oriol A, Nahi H,et al. Daratumumab, Lenalidomide, and Dexamethasone for Multiple Myeloma[J]. N Engl J Med. 2016 Oct 6;375(14):1319-1331.

[14] Targeted New Drug for Multiple Myeloma is Expected to Accelerate Its Marketing, Family Medicines[J].2021,2(5)

[15] CAR T-cell Therapy Impresses in Multiple Myeloma. Cancer Discov. 2018 Feb;8(2):OF2. doi: 10.1158/2159-8290.CD-NB2017-181. Epub 2017 Dec 15. PMID: 29247015.

ISSN: 2664-9640

[16] Zhang Lina, Chen Lijuan, Wang Shuai, Li Jianyong, Zhang Run. Clinical Observation of BCMA Targeted CAR-T Cells in the Treatment of Elderly Patients With Relapsed and Refractory Myeloma [J].Practical Geriatrics,2021,35(01):69-71.

[17] Maus MV, June CH. Zoom Zoom: racing CARs for multiple myeloma. Clin Cancer Res. 2013 Apr 15;19(8):1917-1919.

[18] [18] Martinez M , Moon E K . CAR T Cells for Solid Tumors: New Strategies for Finding, Infiltrating, and Surviving in the Tumor Microenvironment[J]. Frontiers in Immunology, 2019, 10:128.