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Chimeric Antigen Receptor T (CAR-T) Cell Immunotherapy

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Abstract:
Chimeric antigen receptor T (CAR-T) cells are a promising immunotherapeutic modality treating malignant cancer cells. This new approach enables the immune system to identify and attack the malignant cancer cells by expressing a specific antigen on the surface of the T cells.
CAR-T cells have become an encouraging treatment for patients with hematologic malignancies, especially for leukemia and lymphoma. Hematologic malignancies are usually treated using the standard treatments, such as chemotherapy and allogeneic hematopoietic stem cell transplantation.
Targeting solid tumors is more complex than targeting hematological malignancies. However, some clinical trials suggest evidence for the combination of CAR-T and standard treatment being a favorable treatment approach for some specific types of cancer. Examples of these are breast cancer, prostate cancer, colorectal cancer, and gastric cancer.
This review article presents both the CAR-T cells as a promising line therapy for malignant tumors and the challenges of this approach.

Keywords: *CAR-T cell, immunotherapy, cancer, solid tumor, malignancy, antigen surface.*

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I. Introduction:

Chimeric antigen receptor T (CAR-T) cells are a promising immunotherapeutic modality treating malignant cancer cells. This new approach enables the immune system to identify and attack the malignant cancer cells by expressing a specific antigen on the surface of the T cells [1]. This expression enables the T cells to initiate the elimination of the target malignant cells [2].

The T cells are a component of the lymphoid adaptive immune system of the human body and play a crucial role in the immune system by identifying, attacking, and eliminating foreign antigens and infected cells, including cancer cells. The production process of the T cells takes place within the red bone marrow and differentiates in the thymus and lymphoid organs [3] [4].

As mentioned earlier, the human immune system can respond to and eradicate malignant cancer cells. However, the cancer cells can unfortunately develop mechanisms to avoid the immune system [5]. The function of this evasion mechanism is based on the metabolic changes the cancer cells can generate on their surface. The production of a variety of amino acids, lipids, and other chemical compounds can disable the capability of the immune system to identify and destroy the cancer cells [3] [6]. In addition, cancer cells have the secretion ability of suppressive molecules, such as PD-L1, CTLA-4, and other biomarkers, to suppress the T cell activation [3].

Since the mechanisms of the cancer cells and cancer biomarkers together with the lack of success of the standard treatment approaches, for example chemotherapy, radiation, and surgery, have become more comprehensible for us [7], a new method of treatment had to be invented.

Immunotherapy takes many forms in the cancer treatment. Among these therapies are adoptive cell therapies, tumor-infiltrating lymphocyte therapy, engineered T-cell receptor therapy, natural killer cell therapy, immune checkpoint inhibitors, monoclonal antibodies, naked monoclonal antibodies, bispecific monoclonal antibodies, oncolytic virus therapy, cancer vaccines, immune system modulating drugs, immunomodulatory drugs, and the chimeric antigen receptor (CAR-T) cell therapy. The first CAR-T was designed in 1989 at the Weizmann Institute of Science in Israel [9]. The potential of the CAR-T cell has become more encouraging especially after several successes using this new treatment method have been recorded [8].

CAR-T cell design process:
Stage 1: The CAR-T cell treatment starts by isolating the T-cells from the patient through leukapheresis.
Stage 2: The isolated cells are genetically modified by adding receptors to the surface of the T-cell to identify antigens on tumor cells using viral and non-viral methods. As a result, the T-cells become more powerful. The special receptors provide the T-cell the ability to identify the malignant cells, find them, and destroy them.
Stage 3: In this stage the T-cells are already modified and expanded in special cultures in the laboratory.
Stage 4: After passing all the quality tests, the modified T-cells are transferred back to the patient [9] [10].

CAR-T cell immunotherapy for cancer:

CAR-T cells have become an encouraging treatment for patients with hematologic malignancies, especially for leukemia and lymphoma. Hematologic malignancies are usually treated using the standard treatments, for example chemotherapy and allogeneic hematopoietic stem cell transplantation.

The treatment by CAR-T has a proven response rate of up to 90% for relapsed or refractory disease of B-cell acute lymphomata's leukemia (B-ALL). Further, the response rate is up to 60% for patients with B-cell non-Hodgkin lymphoma (NHL). These high response rates are a result of targeting the surface of the malignant cells known as CD19 and CD22 [11] [12].

Moreover, treating ALL, the most common malignancy in the childhood, with CD19 CAR-T cells has demonstrated high remission rates of 90%. In addition, remission has been induced for ALL patients with high risk factors, including patients with Down syndrome, patients positive with Philadelphia chromosome or patients with extramedullary disease, and even patients suffering from a relapse after receiving immunotherapy, such as blinatumomab [13].

After the success of using the CAR-T methods for patients with ALL and NHL, the need for CAR-T treatment for patients with acute myeloid leukemia (AML) has increased. The complete remission rate lies between 60%-80% for younger adults and between 40%-60% for older adults [14]. The AML malignancy presents varying antigens on the surface of the AML cells thus leading to diverse prognoses. The value of CAR-T still needs to be determined in patients with AML malignancy and other hematologic malignancies, such as multiple myeloma [14] [7].

So far, no such cell surface antigens like CD19 and CD22 have been identified for treating solid tumors [15]. Targeting solid tumors is more challenging than targeting hematological malignancies. For cancers like ovarian cancer, renal carcinoma, metastatic neuroblastoma, pancreatic adenocarcinoma, sarcoma, glioblastoma, non-small cell lung cancer, and cholangiocarcinoma, unfortunately, no complete clinical response has been observed. Nevertheless, some clinical trials suggest evidence for the combination of CAR-T and standard treatment being a favorable treatment approach for some specific types of cancer. Examples of these are breast cancer, prostate cancer, colorectal cancer, and gastric cancer [15] [16].

The challenges of the therapy for solid tumors using the CAR-T approach connect back to the tumor microenvironment barriers, for instance the tumor antigen heterogeneity. Tumors have different levels of antigen expression at the tumor sites. These various antigens complicate the ability of the CAR-T to identify the tumor cell specific antigen. In addition, in hematological cancers, the CAR-T has more contact with the malignant cells in the blood and lymphatic system than in solid tumors, whereas in solid tumors the penetration is limited by the tumor endothelium. Another important challenge in the solid tumor is the immunosuppressive tumor microenvironment. Solid tumors have diverse malignant cells supporting the tumor growth, angiogenesis, and metastasis [16].

Toxicities with CAR-T cell therapy:
Cytokine release syndrome (CRS):
CAR-T can cause substantial toxicities. One significant toxicity is cytokine release syndrome (CRS) [17]. CRS is a common toxicity associated with CAR-T. CRS triggers an inflammatory response caused by the release of excessive levels of cytokines after CAR-T infusion. CRS can impair the activity of organs and systems in the patient, and could endanger his life [18].
CRS is measured by clinical laboratories. The grade ranges from mild to severe CRS, and ultimately to life-threating CRS [19].
Grade 1: mild CRS; not life-threatening, requires only symptomatic treatment.
Grade 2: moderate CRS; requires intervention. Oxygen requirement <40% or hypotension responsive to fluids or low dose vasopressor, or grade 2 organ toxicity with organ dysfunction.
Grade 3: severe reaction; requires aggressive intervention. Oxygen requirement >40% or hypotension requiring high dose or multiple vasopressors, or grade 3 organ toxicity.
Grade 4: life-threatening; requires for ventilator support or grade 4 organ toxicity [20].
Usually, the first sign of developing a CRS is a high body temperature in the first 1-2 days after the infusion of the CAR-T [20]. Examples of additional symptoms are hemodynamic instability, tachycardia, hypotension,

capillary leak, and cardiac dysfunction. In addition, nausea, myalgia, fatigue, renal failure, hepatic failure, and disseminated intravascular coagulation may occur [18] [19] [20].

Neurologic toxicity:

The development of neurologic toxicity has been reported after receiving CAR-T cells. It involves the appearance of new neurological signs or symptoms within the first 1-3 weeks of infusion after receiving CAR-T cells. Signs and symptoms including delirium, aphasia, obtundation, myoclonus, seizure, headache, language disturbance, ataxia, weakness, peripheral neuropathy, and visual change have been reported after receiving CAR-T cells [19] [20].

The management of toxicities has become an integral step in the successful clinical application of CAR-T cells. The first line therapy after developing CRS is to use anti- interleukin-2 (IL-2) receptor antibody tocilizumab. Tocilizumab is a monoclonal antibody against membrane-bound and soluble IL-2. In addition, according to the severity of the CRS, the use of corticosteroids should be considered [13] [19] [20].

II. Summary:

Immunotherapy has emerged as a new mainstay of treatment for various cancers. There is significant research worldwide in order to develop a new approach and to increase the efficacy of the CAR-T cell therapy. CAR-T has become an effective regimen for treating hematological malignancies. Despite the successes in treating hematological malignancies, the CAR-T cells have encountered significant challenges in treating solid tumors. Although progress has been reported in treating some solid tumors, the major challenge still lies in the microenvironment of the solid tumor, including the malignant activity of the tumor cells. Consequently, there is a need for increased knowledge on the changes in the microenvironment of the solid tumor and for the development of a new approach for an effective and safer therapy with armored CAR-T cells.

References

[1]. Miao L, Zhang Z, Ren Z, Tang F, Li Y. Obstacles and Coping Strategies of CAR-T Cell Immunotherapy in Solid Tumors. Front Immunol. 2021 May; 12:687822. https://doi.org/10.3389/fimmu.2021.687822

[2]. Kosti Paris, Maher John, Arnold N. James. Perspectives on Chimeric Antigen Receptor T-Cell Immunotherapy for Solid Tumors. Frontiers in Immunology. 2018 May; Vol: 9. https://doi.org/10.3389/fimmu.2018.01104

[3]. Gonzalez Hugo, Hagerling Catharina, Werb Zena. Roles of the immune system in cancer: from tumor initiation to metastatic progression. Genes & Dev. 2018; 32: 1267-1284. doi:10.1101/gad.314617.118

[4]. Fabbri M, Smart C, Pardi R. T lymphocytes. The International Journal of Biochemistry & Cell Biology. 2003 July; Vol 35, Issue 7; P: 1004-1008. https://doi.org/10.1016/S1357-2725(03)00037-2

[5]. Ribas A. Adaptive immune resistance: How cancer protects from immune attack. Cancer discovery. 2015 September; 5(9):915-919. https://doi.org/10.1158/2159-8290.CD-15-0563

[6]. Villaba Martin, Rathore G. Moeez, Royuela-Lopez Nuria, Krzywinska Ewelina. Et.al. From tumor cell metabolism to tumor immune escape. 2013 January; Vol: 45, Issue 1; P: 106-113. https://doi.org/10.1016/j.biocel.2012.04.024

[7]. Adaniya S.S, Cohen D. A., Garfall L. A. Chimeric antigen receptor T cell immunotherapy for multiple myeloma: A review of current data and potential clinical applications. American Journal of Hematology. 2019 February; P: S28-S33. https://doi.org/10.1002/ajh.25428

[8]. Smith J. Aaron, Oertle J, Warren D, Prato D. Chimeric antigen receptor (CAR) T cell therapy for malignant cancers: Summary and perspective. Journal of Cellular Immunotherapy. 2016 November; Vol: 2, Issue 2; P: 59-68. https://doi.org/10.1016/j.jocit.2016.08.001

[9]. Sabbah Mohammad. Immunotherapy: The next generation of cancer treatment. International Journal of Medical Studies. 2022; 7(6), 1-10. https://www.ijmsonline.in/index.php/ijms/article/view/227

[10]. Miliotou, Androulla N. Papadopoulou, Lefkothea C. CAR T-cell Therapy: A New Era in Cancer Immunotherapy. Current Pharmaceutical Biotechnology. 2018; Vol: 19; Number 1; p: 5-18(14). https://doi.org/10.2174/1389201019666180418095526

[11]. Halim L, Maher J. CAR T-cell immunotherapy of B-cell malignancy: the story so far. Therapeutic Advances in Vaccines and Immunotherapy. 2020, Vol. 8: 1–17. DOI: 10.1177/2515135520927164

[12]. Jing P, Qing N, Biping D, Shuangyou L. et.al. . CD22 CAR T-cell therapy in refractory or relapsed B acute lymphoblastic leukemia. Leukemia. 2019 May; 33, p: 2854–2866. https://doi.org/10.1038/s41375-019-0488-7

[13]. Pehlivan C. K, Duncan B. B, Lee W. D. CAR-T Cell Therapy for Acute Lymphoblastic Leukemia: Transforming the Treatment of Relapsed and Refractory Disease. Current Hematologic Malignancy Reports. 2018 August; 13; P: 396–406. https://doi.org/10.1007/s11899-018-0470-x

[14]. Hofmann S, Schubert M.L, Wang L, Bailin H. et.al. Chimeric Antigen Receptor (CAR) T cell Therapy in Acute Myeloid Leukemia (AML). Journal of Clinical Medicine. 2019 February; 8(2):200. https://doi.org/10.3390/jcm8020200

[15]. Li J, Li W, Huang K, Zhang Y. et.al. Chimeric antigen receptor T cell (CAR-T) immunotherapy for solid tumors: lessons learned and strategies for moving forward. Journal of Hematology & Oncology. 2018 February; Vol: 11; number: 22. https://doi.org/10.1186/s13045-018-0568-6

[16]. Marofi F, Motavalli R, Safonov A.V, Thangavelu L. et.al. CAR T cells in solid tumors: challenges and opportunities. Stem Cell Research & Therapy. 2021 January; Vol: 12; number: 81. https://doi.org/10.1186/s13287-020-02128-1

[17]. Rossig C. CAR T cell immunotherapy in hematology and beyond. Clinical Immunology. 2018; Vol; 186; P: 54-58. https://doi.org/10.1016/j.clim.2017.09.016

[18]. Thanindratarn P, Dean D.C, Nelson S.D.et.al. Chimeric antigen receptor T (CAR-T) cell immunotherapy for sarcomas: From mechanisms to potential clinical applications. Cancer Treatment Reviews. 2020 January; Vol: 82: 101934. https://doi.org/10.1016/j.ctrv.2019.101934

[19]. Chalice B.L, Hollie J.J, Renier B.J, Kevin K.J. Toxicity and management in CAR T-cell therapy. Molecular Therapy Oncolytics. 2016; Vol: 3; 16011. https://doi.org/10.1038/mto.2016.11
[20]. Hirayama V. Alexander, Turtle J. Cameron. Toxicities of CD19 CAR-T cell immunotherapy. American Journal of Hematology. 2019 February; P: S42-S49. https://doi.org/10.1002/ajh.25445

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