New Developments in the Therapy Using Chimeric Antigen Receptor T Cells for the Treatment of Breast Cancer

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Abstract

The most prevalent cancer that poses a major threat to women's lives worldwide is Breast Cancer (BC). Clinically, a need to create new and efficient methods for the effective treatment of BC is supported by the high incidence of different resistance to current therapeutic treatments. One of the immunotherapies, the chimeric antigen receptor T (CAR-T) cells therapy, has proven to have a potent ability to target and destroy tumours. The effectiveness of CAR-T cells therapy has been investigated in a number of human diseases, including breast cancer, as a result of the efficacy of CAR-T therapy in treating haematological malignancy. This study provided an overview of the state of CAR-T treatment for breast cancer, including its developments, difficulties, and potential solutions in both clinical and research settings. The effects of potential antigen targets, the tumour microenvironment, immune escape, and the pairing of CAR-T therapy with other therapeutic approaches to further increase CAR-T treatment's therapeutic success were also highlighted. As a result, our analysis offered a thorough grasp of CAR-T cell therapy in the treatment of breast cancer, which will spark intense interest in further, in-depth research on CAR-T based therapy.

Keywords: CAR-T cells • Tumor microenvironment • Immunotherapy • Combined therapy

Introduction

According to the World Health Organization, female breast cancer will be the most often reported malignancy in 2020. Every 14 seconds, a woman will receive a breast cancer diagnosis somewhere in the world. In 185 countries throughout the world, BC is the most often diagnosed cancer and the primary cause of cancer death in women, accounting for 24.5% of new cases and 15.5% of fatalities. BC is divided into five subtypes: luminal A-like, Luminal B-like HER2-, Luminal B-like HER2 +, HER2- enriched, and Triple Negative Breast Cancer (TNBC). These subtypes are determined by the states of the oestrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2), and proliferation marker protein Ki-67. The diagnosis and prognosis of the condition are closely tied to the classification. The characterisation of molecular hallmarks has advanced quickly, which has greatly enhanced breast cancer treatment. Surgery, endocrine therapy, chemotherapy, targeted treatments, radiation, and systemic medicines are only a few of the key therapeutic options for BC. Advanced malignant breast cancer is still difficult to treat with the existing therapeutic options, nonetheless. Investigating alternative and cutting-edge therapies for breast cancer is therefore important. Chimeric antigen receptor (CAR) T cell therapy has been successful in treating a number of tumours in recent years. The genetically engineered CAR-T cell treatment is a promising adoptive cellular immunotherapy that has shown a potent ability to kill tumour cells and mediate cytotoxic effects. Acute Lymphoblastic Leukaemia (ALL), lymphoma, and multiple myeloma are just a few of the malignant disorders that are now being treated by CAR T cells. The

following phases make up the core CAR-T cell treatment technique. Prior to being transfected with a viral or non-viral vector carrying a reprogramming CART for targeted identification, T cells from patients' peripheral blood are first collected. Second, to increase the number of modified T cells needed for therapeutic use, their populations were in vitro expanded. The human body was then reinfused with the altered CAR-T cells. As long as the CAR T cells are delivered correctly, they should be able to recognise the target antigen, multiply, and assault the tumour cells, leading to tumour remission with a persistent effect. Recently, CAR-T therapy for the treatment of breast cancer underwent extensive research and made significant advancements. Yet, some patients are still unresponsive to CAR-T therapy, necessitating further, in-depth research to uncover the precise reasons. The review evaluated and discussed the current state of CAR-T treatment for breast cancer, including developments, obstacles to overcome, and potential solutions. Furthermore highlighted were the functions of possible antigen targets, the tumour microenvironment, immune escape, and combination therapy approaches with CAR-T to further increase the therapeutic efficacy of CAR-T. The Extracellular Domain (ECD), hinge region, Transmembrane Domain (TMD), and intracellular domain are the four core segments that make up CARs (ICD). The most traditional element of ECD is a Single-Chain Variable Fragment (scFv), which is obtained from antibodies and is arranged as mutable heavy (VH) and Light (VL) chains. ECD is an Antigen Binding Domain (ABD).The role of ECD includes CAR function prediction and tumor antigen recognition independent from the presentation of major Histocompatibility Complex (MHC) .Hinge region (spacer) is a linker between ECD and TM. Spacer has the capability of distance adjustment by differences in the length and flexibility which can profoundly affect binding affinity.TM is usually derived from CD3ζ, CD4, CD8, or CD28 molecules between spacer and ICD as an anchor to the cell membrane. The ICD, which consists of an activation domain and a costimulatory domain, is arguably the most crucial component of CARs since it allows T cells to convey two signals for complete activation and perform effector activities. The process that has led to the revolutionary developments in generational CAR T-cells is the ongoing innovational modification of ICD. The CD3 intracellular domain, which is made up of immune receptors' tyrosine-based activation patterns, is present in the first generation of CARs (ITAMs). CAR-T cells, however, shown a limited capability for proliferation and endurance in vivo throughout clinical studies, which resulted in tumour recurrence. T cell proliferation and differentiation are driven by full activation of T cells, which depends on dual signal activation by antigenic and costimulatory signals as well as the activity of cytokines. The second generation of CARs adds a costimulatory domain, like CD28 or 4-1BB, to the traditional signal of T cell activation to help effectively inhibit tumour growth. The cytotoxicity against tumours is further improved with the addition of one more (for a total of 2) costimulatory domain in the third generation of CARs. Inducible costimulatory molecule (ICOS), OX40 (also known as CD134), CD40, and other costimulatory molecules have recently been found. The nuclear factor of activated cells (NFAT) domain was added to the second-generation CARs in the fourth generation, also known as T Cells Redirected for Universal Cytokine Killing (TRUCKTs), with the primary goal of overcoming obstacles in the Tumour Microenvironment (TME). In order to increase the capacity of T cells, TRUCKTs either added IL-12 and IL-18, IL-7, IL-15, and IL-21, or C-C motif chemokine 19 (CCL-19) and CCL-21, which attract immune cells including NK cells, macrophages, and CAR-T cells to the tumour. . The fifth generation of CAR-T cells is currently being developed and tested for both efficacy and safety. Since they can activate the JAK-STAT signalling pathway to regulate CAR T cell growth and activation, CARs containing an additional IL-2 Receptor-Chain Fragment (IL-2R) were frequently employed. One of the most effective immunotherapies, CAR-T cell therapy is the first line of treatment for a number of hematologic illnesses. However, the high heterogeneity of cancer cells, complex tumour microenvironment, and minor

immune escape, which distinguish breast cancer from blood illnesses, pose a number of challenges and insurmountable obstacles that limit the therapeutic efficacy of CAR-T cells treatment in treating breast cancer. Thus, we talked about the potential for high tumour heterogeneity in this part.This refers to the spatial and temporal extent of diversity within primary tumours and metastatic sites. Also, it might occur as a result of mutational contents that represent a past process of alterations that continuously accumulated during the growth of the tumour. Due to its extreme heterogeneity, BC can be divided into a wide range of distinct subtypes. TNBC can also be further split into 6 subtypes: 2 Basal-Like (BL1 and BL2), Immunomodulatory (IM), Mesenchymal (M), Mesenchymal Stem-Like (MSL), and Luminal Androgen Receptor (LAR) subtypes. TNBCs were recently divided into four transcriptome-based subgroups by Jiang et al., including Luminal Androgen Receptor (LAR), immunomodulatory, basal-like immune-suppressed, and mesenchymal-like. Depending on the breast cancer subtype, BC has a different prognosis and course of treatment. Furthermore, the antigens expressed on the surface of tumour cells vary in kind and intensity and are subject to temporal and spatial variability. Hence, the widespread use of CAR-T cell treatment in BC is constrained since it is very challenging to locate a Tumour Specific Antigen (TSA) like CD19 used to haematological malignancies. The Tumour Microenvironment (TME) encompasses several stages of a tumor's growth, including its start, progression, and metastasis, and it creates an almost endless dynamic variation in the host tissues. TME is made up of a variety of elements, such as immune cells with antitumor properties, immunosuppressive cells, matrix components,vasculature, soluble substances that are beneficial to angiogenesis, epitope masking, a hypoxic environment, and low pH conditions. TME thereby hastens tumour development, proliferation, differentiation, and metastasis, which may lead to T cell malfunction and ineffectiveness of CAR-T cell therapy. The clinical potential of immunotherapies is being undermined by immunological suppression in TME, according to mounting evidence. The trafficking, infiltration, persistence, and activities of associated effector CAR-T cells are constrained by complex interactions between tumour cells and TME components. The rapid advancement of single-cell sequencing technology and biotechnology has made it possible to accurately compare and analyse the differences in single-cell transcriptomes, genomes, and epigenetic alterations between primary and metastatic tumours as well as circulating tumour cells, providing a brand-new way to study the distinctive characteristics of tumour cells. Hence, the next sections will go into great detail about immunosuppressive cells in TME.

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