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Chimeric antigen receptor T-cell as a significant player in the innovative treatment of hematological cancers

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Abstract:

Introduction and purpose:

Chimeric antigen receptor-T (CAR-T) cells have achieved inspiring outcomes in the treatment for lymphoid malignancies, especially diffuse large B-cell lymphoma (DLBCL) and acute lymphoblastic leukemia (ALL), providing alternative therapeutic options for patients who failed to respond to conventional treatments. CAR-T are based on the patient's T lymphocytes, which through genetic modification, gain new abilities to detect and fight cancer cells. Although the percentage of complete remissions after standard treatment of B-cell malignancies is quite high, methods that could have an even better result regarding patient survival by reducing the side effects of treatment are still being sought to improve the quality of patients' lives. CAR-T is a culmination of many years of research in the dynamically developing area of immunotherapy as a revolutionary therapy of hematological cancers treatments.

State of knowledge:

In order to explore the topic, analysis included research available in the PubMed database. The research focused on the possibility of using CAR-T cell therapy in selected hematological cancers.

Conclusion:

CAR-T is one of the most advanced and personalized methods of immunotherapy. Despite the side effects of this method, there is still scope for improvement. Our overview summarizes all the issues that have been overcome in designing this therapy, as well as highlighting all the challenges that still need to be addressed.

Keywords: CAR-T, immunotherapy, mechanisms, strategies, treatment

Introduction and purpose:

The immune system has two parts: the innate (non-specific) and adaptive (specific) immune systems. The mechanisms of innate immunity work very quickly, but they are not as precise and represent the first line of defense against pathogens. The adaptive immune systems are more specific and consist of two key cells of the immune system, which are called B-cells and T-cells, derived from hematopoietic stem cells in the bone marrow [1].

B-cells are involved in the humoral immune response, whereas T-cells are involved in cell-mediated immune response. B-cells are responsible for the creation of antibodies, opsonization and destruction of pathogens and providing immunological memory [2].

T-cells are central players in the immune response to infection. When the cell becomes infected and cell-mediated immunity is needed, T-cells respond by eliminating the infected cell.

There are three main groups of T-cells based on their function: helper, regulatory, and cytotoxic T-cells.

Once stimulated by the appropriate antigen, helper T-cells secrete cytokines, which stimulate the differentiation of B-cells into plasma cells, thereby causing antibody production. The immune response is controlled by regulatory T-cells, and in turn, cytotoxic T-cells recognize and destroy foreign cells and tissues [3].

The cells exchange information on an ongoing basis. T-cell and B-cell lymphocytes work together to recognize foreign substances called antigens. Every second, there are a billion interactions between B-cells and T-cells.

When B- or T-cells spot the same antigen, it triggers a huge alert. The T-cells and particularly B-cells increase in number extremely quickly, which targets the same antigen. The immune system is truly remarkable, as it is not just like an army that helps to defend the body against dangerous infections from the outside, but it also

helps to protect against cells within the body that can develop potentially dangerous mutations [4]. Sometimes this process fails, which is when cancer cells are caused by a mutation. Under the correct conditions, the mutated cell should be captured and undergo apoptosis, otherwise it will result in the development of cancer, which is the continual unregulated proliferation of cancer cells.

Chimeric antigen receptor (CAR) is a modified receptor involved in reprogramming and redirecting patients ′T-cells to a precise target and destroying tumor cells [5]. It represents a significant breakthrough in personalized immunotherapy and genetic engineering used primarily in the treatment of hematological cancers especially, Diffuse Large B-cell Lymphoma (DLBCL) and Acute Lymphoblastic Leukemia (ALL).

Description of state of knowledge:

On 30 August 2017, the US Food and Drug Administration (FDA) approved Tisagenlecleucel, a product of anti-CD19 CAR-T-cells as a first CAR-T therapy for patients up to 25 years of age with refractory B-cell precursor acute lymphoblastic leukemia (BCP-ALL) or in second or later relapse. The treatment has shown remarkable outcomes based on preliminary results from the phase 2 multicenter ELIANA trial [6]. This study showed an impressive 60% complete remission rate and 81% overall response rate (ORR) in 75 children and young adults [7]. In May 2018, the FDA approved Tisagenlecleucel also for treatment of relapsed and refractory lymphoma, where the JULIET trial showed a high rate and duration of response to Tisagenlecleucel therapy among adult patients with relapsed or refractory DLBCL. The results were very promising, with a best overall response rate of 52% [8].

Another anti-CD19 CAR T-cell therapy, Axicabtagene ciloleucel, was approved in October 2017 as a first CAR T-cell therapy for lymphoma with complete responses noted in 58% patients ′results from the phase 2 multicenter ZUMA-1 trial. In contrast to Tisagenlecleucel, Axicabtagene ciloleucel had a higher objective response, complete response, and overall survival but had higher grade cytokine release syndrome (CRS), and both products had similar neurologic events [9, 10].

In February 2021, the FDA approved Lisocabtagene maraleucel as a new CD19-directed chimeric antigen receptor CAR-T cell therapy for patients with refractory or relapsed Large B cell Lymphomas (LBCL) who had undergone two or more lines of systemic therapy. Data from the TRANSCEND clinical trial has shown that Lsocabtagene maraleucel can lead to rapid and sustained remission with a low incidence of all grades and severe cytokine release syndrome and neurological events among patients at high risk of relapse or refractory to high-dose therapy lymphocytes B lymphomas [11].

Structure of CAR-T cells:

CAR contains four modules: an extracellular antigen recognition domain, a hinge region, a transmembrane domain, and one or more intracellular T-cell signaling domains. An antigen recognition domain of the single-chain variable fragment (scFv) is a chimeric protein. It consists of both light and heavy immunoglobulin chains that are linked by a peptide linker [12]. The variant of the selected heavy and light immunoglobulin chains depends on their ability to bind to the associated CD19-target [13,14]. The CD19 antigen is a transmembrane glycoprotein that takes part in regulation B lymphocyte activation and proliferation. CD19 expression in normal tissues is restricted to B lymphocyte lines and is maintained at high levels in most B-cell hematologic malignancies [15]. The CD19 CAR-T cell therapy is the most thoroughly studied product in CAR-T cell therapy and shows a high effectiveness in treatment of malignant B cell tumors.

Production of CAR-T Cells:

To qualify for CAR-T-cell therapy, a patient must fulfill a number of eligibility criteria and undergo conditioning chemotherapy to ensure CAR T-cells are not rejected by reducing the number of T lymphocytes [16]. To reprogram the patient′s own T-cell to express the chimeric antigen receptor (CAR), the patient's blood is harvested so that the T-cell can be isolated and activated in the lab. A genetically engineered CAR fusion protein is inserted into the genome of these cells using lentiviral or retrovirus vector, so the T-cell produces the surface receptor CAR [16,17]. Then the T-cells that stably express CAR are isolated and expanded. Only those stable CAR-T cells can recognize and attach a specific marker protein on the cancer cell surface and signaling its destruction [18].

Limitations of CAR-T Cells:

Despite a number of clinical successes, CAR T-cells have some limitations, including tumor antigen escape, the immunosuppressive microenvironment, CAR T-cell exhaustion and decreased persistence [19]. The most challenging problem is the development of tumor resistance to single antigen targeting CAR constructs. This is due to mutations in the genes which could destroy the cognate epitope recognized by the anti-CD19 scFv, making the tumor cells no longer noticeable to CD19 CAR-T [20]. At the beginning, single antigen targeting CAR-T cells can deliver high response rates, but later the malignant cells of a significant portion of patients treated with these CAR-T cells display either partial or complete loss of target antigen expression of the CAR T-cells that are targeted, which is called CD19 loss [20,21].

However, CAR T-cell therapy is not without side effects. T-cell therapy is given once, which is why most possible complications occur within the first one to two weeks following the CAR-T cell infusion. They are usually temporary and can be resolved with medication, but in some cases, the complications can be life-threatening. Of these, the most common and serious are cytokine release syndrome (CRS) and neurotoxicity. There are many factors that influence the intensity of CRS. It depends on the type of therapy or even the characteristics of the patients [22].

CRS is a direct result of the immune system fighting cancer cells, manifested by fever, drop in blood pressure, shortness of breath, muscle or joint pain and fast heart rate. Symptoms of neurotoxicity in the course of CAR-T therapy include confusion, delirium, expressive aphasia, encephalopathy [23,24].

Availability of CAR T-cells therapy in Poland:

Despite its high effectiveness, CAR T-cell therapy is still a last resort therapy because of very high costs. Due to the specificity of the preparation and administration of CAR-T therapies, their use requires the appropriate infrastructure of the center and training of specialists. Currently, there are 4 certified centers in Poland where CAR-T therapy can be administered to patients.

By the decision of the Minister of Health, from September 1, 2021, CAR-T therapy is reimbursed by the Narodowy Fundusz Zdrowia (NFZ) in the treatment of relapsed or refractory B-cell acute lymphoblastic leukemia in children and adults up to 25 years of age.

Summary:

CAR-T cell therapy is the culmination of many years of research, which represents a breakout in personalized cancer treatment. Clinical outcomes of CAR-T cell therapy in patients with hematologic malignancies are remarkable because of the results, including the response rates where 90% of patients go into deep remission and potentially 60% of patients can be cured with this therapy. Unfortunately, due to the high cost of therapy and potential risk of toxicity, it still needs to be the subject of intensive scientific research in order to improve the specificity, efficacy, and safety of CAR T-cell therapy.

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