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Immunotherapy and cell therapy as a practical approach in cancer therapy

Sogand Vahidi [1], Seyedeh Elham Norollahi [2], Ali Akbar Samadani [3,4] *

[1] Medical Biology Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran

[2] Cancer Research Center and Department of Immunology, Semnan University of Medical Sciences, Semnan, Iran

[3] Department of Basic Medical Sciences, Neyshabur University of Medical Sciences, Neyshabur, Iran

[4] Guilan Road Trauma Research Center, Guilan University of Medical Sciences, Rasht, Iran

Abstract

Cancer treatment is one of the most important challenges in medical science. Most methods such as surgery, chemotherapy, and radiation therapy are not completely effective in treating cancer. In this way, immunotherapy and cell therapy have revolutionized cancer treatment. Immunotherapy and cell therapy, like chemotherapy, are given systemically and are effective in preventing the spread of malignancies, but in contrast, they only attack malignant cells and have little effect on their cells, and are more specific. Slowly They have completely different efficiencies depending on the different types of immunotherapy, which include selective cell transfer (ACT) and immunosuppressive inhibitors (ICIs). The study of the mechanisms underlying the escape of cancer cells from the immune system is also very important in identifying new cancer treatments. This review discusses the types of immunotherapy and cell therapy in cancer, the history of development, and recent findings on the penetration of immune cells into the tumor and its relationship to cancer immunotherapy, focusing on new studies and its potential clinical applications.

Keywords: Cancer immunotherapy, Immune system, Tumor, Therapy

*Corresponding Author: Ali Akbar Samadani

✉ Email: a_a_hormoz@yahoo.com

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Introduction

Cancer, the most dangerous disease, kills millions of patients. Comprehensive knowledge of cancer biology allows researchers to design more appropriate treatment systems. The type of treatment depends on the type of cancer and the progress and purpose of the treatment. Surgery is the first option for the direct removal of tumors in an area. Radiotherapy destroys tumors by damaging the DNA of cancer cells. Chemotherapy helps reduce or stop the growth of tumors by using highly toxic drugs. Immunotherapy involves the use of monoclonal antibodies, cancer vaccines, and acceptor cell transfusions. It has now become an important treatment for cancer with acceptable clinical results (1, 2). In addition, stem cell therapy has provided a promising option in the fight against cancer (3). Due to the increased targeting of tumors, the therapeutic effect of other treatments has improved. Many stem cell-based strategies have already been clinically tested and have great achievements and challenges in the field of cancer. Therefore, further evaluation is needed to prepare these methods for clinical trials (4, 5). In addition, in the event of persistent or recurrent disease, a small number of treatment strategies can eliminate the remaining malignant cells and treatments that are more effective. There is much evidence to support the vital role of the immune system, especially lymphocytes, in controlling and eradicating cancer. Inhibiting the immune system to achieve clinical efficacy has been the focus of many treatments (6, 7). More than two decades have passed since Gross and colleagues demonstrated the principle of genetic alteration of cytotoxic T lymphocytes into tumor cells, and have done their main work by stating that chimeric T cell receptors with anti-tumor properties can test this method in the fight against tumors. Provides humanity, passes (8). On the other hand, in the last decade, the role of the immune system in controlling tumorigenesis and tumor progression has been well established. Although the role of adaptive immune responses (e.g., mediated by lymphocytes) has been widely expressed, the function of innate immune responses is less well known. The collected evidence shows a correlation between tumor permeable lymphocytes (TIL) in cancerous tissue and favorable prognosis in malignant types (9, 10).

A key factor in the limited response seen in various experiments is the complexity of immune-host tumor interactions and the existence of several redundant tumor-mediated immune suppression mechanisms. It is also essential to have a thorough understanding of the principles of tumor antigen production/maintenance, antigenic evolution, and tumor immunity heterogeneity. Further efforts in basic research should also clarify the structure and function of most regulatory immune pathways and their specific role in various human malignancies (11).

Understanding the dynamic interactions between tumor cells and the immune system allows us to specialize in immune therapies and design optimal combination approaches to improve outcomes in patients with advanced malignancy. In a study by Samadani et al. 2020, the main programs optimized for the treatment of CAR-T cancer cells were classified and reviewed. The results showed that immunotherapy of cancer by CAR-T cells (chimeric antigen receptor (CAR) T-cell therapy) has significant clinical potential in malignancies. In other words, it is a good cancer treatment. CAR is a specific recombinant protein compound that targets the structure of antibodies to activate T cells. CAR-T cells can kill B cell malignancies (12). Therefore, research on the risks as well as strategies to neutralize the possible consequences of the tumor is of great importance, as successful protocols and strategies in the treatment of CAR-T cells can improve the efficiency and safety of cancers (Table 1).

Table1. CAR T-cell therapies accepted by FDA.

Targeted antigen	Name	Target disease	Patients
BCMA	Ciltacabtagene autoleucel	Multiple myeloma	Adults with multiple myeloma
	Idecabtagene vicleucel	Multiple myeloma	Adults with multiple myeloma
CD19	Tisagenlecleucel	B cell non-Hodgkin's lymphoma	Children and young adults with

	(NHL) / B cell acute lymphoblastic leukemia	B cell acute lymphoblastic leukemia
Brexucabtagene autoleucel	B cell non-Hodgkin's lymphoma (NHL)	Adults with B cell non-Hodgkin's lymphoma (NHL)
Lisocabtagene maraleucel	B cell non-Hodgkin's lymphoma (NHL)	Adults with B cell non-Hodgkin's lymphoma (NHL)
Axicabtagene ciloleucel	Follicular lymphoma / Non-Hodgkin's lymphoma (NHL)	Adults with follicular lymphoma and NHL

A study by Chu in 2020 examined the mechanisms for using different types of stem cells in the treatment of cancer. Recent advances in the clinical applications of stem cells as well as the common risks of this treatment have been summarized. Depending on their inherent capacities, different types of stem cells have been used for anti-cancer treatment. HSC transplantation has provided an effective treatment for cancers such as leukemia, multiple myeloma and lymphoma. Simultaneous injection of mesenchymal stem cells leads to modulation of the immune system, high effects in reducing cases of graft-versus-host disease (GVHD) and also repair of damaged tissues after heavy chemotherapy or radiotherapy. The defined induction protocol enables the production of a large number of clinically world-class immune cells for further evaluation in humans. Finally, targeting CSCs with the delivery of CSC and PSC antigen-derived anticancer vaccines may provide promising strategies to prevent tumor growth, metastasis, and recurrence. As a result of this research, to improve the overall results in the fight against cancer, guidelines for the future are presented (13).

In a study by Miliotou et al. 2018, concerning several conventional cytotoxic methods for neoplastic diseases and their limited effectiveness according to the heterogeneity of cancer cells, a study was conducted for better treatment approaches such as immunotherapy. Increases the patient's immunity. CAR-T cell therapy involves the genetic modification of a patient's autologous T cells to express a specific CAR for a tumor antigen (Figure 1). Clinical trials have shown very promising results in patients in the final stage with a complete recovery of up to 92% in acute lymphocytic leukemia (14).

In a study by Saadatpour et al. in 2017, they examined cell therapy and gene therapy and imaging techniques. Studies have shown that cancer is one of the most important health problems in the world and has created many challenges; the current understanding of this disease is very useful in the emergence of a number of new treatments. Among these, cell therapy and gene therapy are known as new and effective therapies. One of the major challenges of cell therapy and gene therapy in cancer is the proper monitoring of modified cells and genes. Visual tracking of cell therapy, immune cells, stem cells and genetic vectors containing therapeutic genes and various drugs is important in the treatment of cancer. Similarly, molecular imaging such as nanosystems, fluorescence, bioluminescence, positron emission tomography, and photon emission computed tomography has also been identified as powerful tools in monitoring cancer patients receiving cell therapy and gene therapy or drugs (15).

A 2016 study by Velcheti et al. Focused on the basic principles of immunotherapy, new pathways, and hybrid immunotherapy. This study showed that the recent success of immunotherapy strategies such as blockade of immunosuppression in several malignancies has highlighted the role of immunotherapy in the treatment of cancer. Cancers use several mechanisms to select host-tumor immune interactions that lead to escape from the immune system. Our understanding of host tumor interactions has evolved over the past few years and has led to promising new treatment strategies (16).

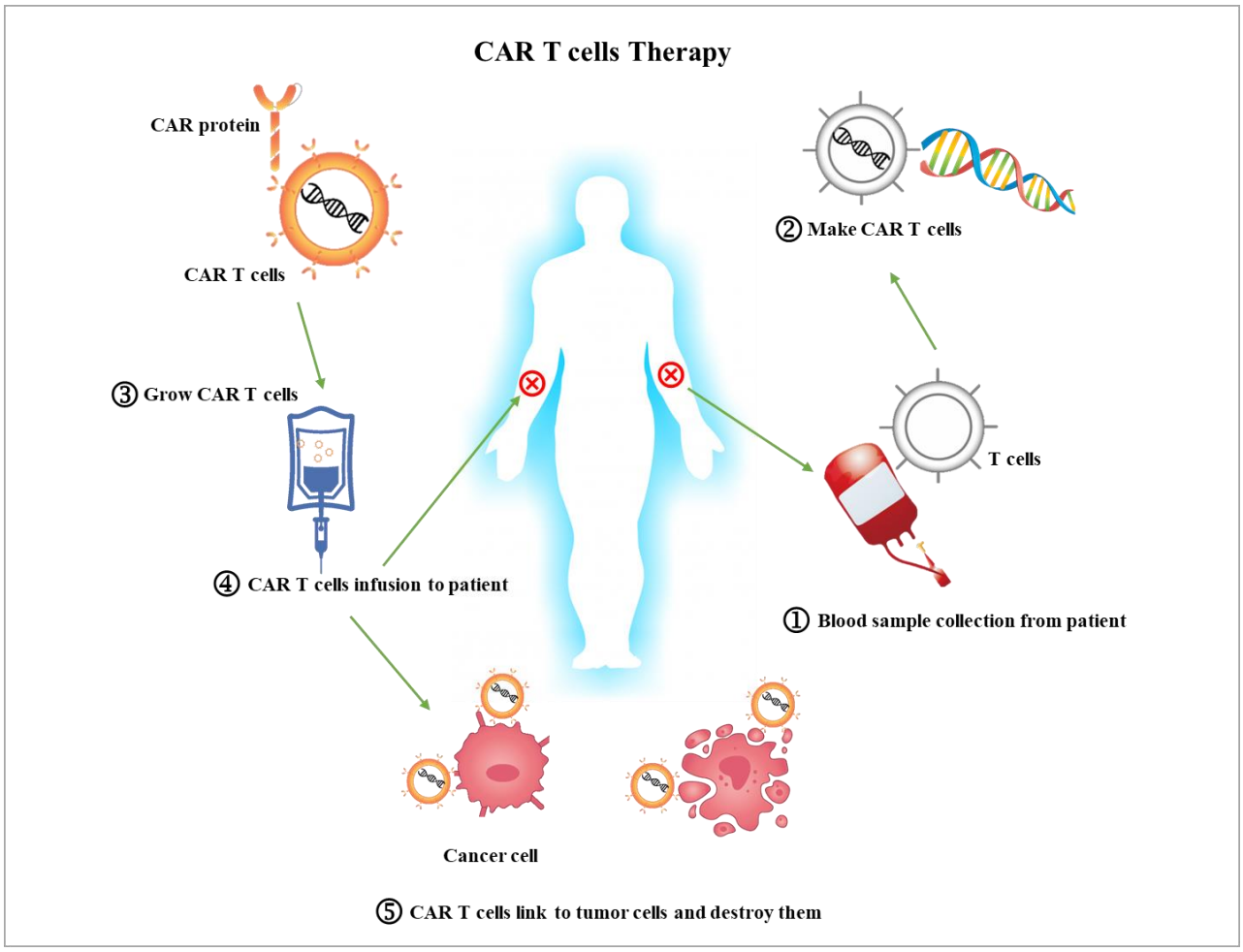

Figure 1. General mechanism of CAR T cells therapy.

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The occurrence of molecular remission after donor lymphocyte infusion (DLI) in myeloid tumours relapsing after bone marrow transplantation was the first demonstration of the usefulness of adoptive T cell therapy (ATC) in human cancers (17). Increasingly broad tumor infiltrating lymphocytes (TIL) have also been shown to implementation details and long-term transformation of large vascularized metastatic melanomas (18). In numerous EBV-associated cancers, such as Hodgkin's disease, Burkitt's lymphoma, and nasopharyngeal carcinoma, ATC utilizing Epstein-Barr virus-specific T cells demonstrated clinical benefit (19). Furthermore, once circulating tumor-reactive T cells from a patient's peripheral blood were ex vivo increased in acceptable numbers and administered to the patients, therapeutic efficacy was observed (20). Whereas these treatments depend on endogenous T cell repertoires, technical developments in T cell engineering with retroviral and plasmid vectors have enabled the genetic introduction of tumor specific T cell receptors (TCRs) or CARs to generate large numbers of tumor targeting T cells. Unlike TCRs, that either acknowledge peptides obtained from cellular proteins introduced in the context of the major histocompatibility complex (MHC), CARs identify any

surface antigen, such as carbohydrates and phospholipids, with elevated MHC independent identification. Hematological malignant tumors are the focus of about 65 percent of the research (21). Whereas CD19 is the most commonly targeted antigen in hematological B-cell tumours (>80%), research is ongoing to look into other antigens also including ROR1, B-cell maturation antigen, CD20, CD22, CD30, CD33, CD123, CD133 and CD138 (22). Patients with various B-cell cancers have been considered with CD19 CAR T cells in research trials (Figure 2), and while solid tumors were the first targets of CAR T cell treatments (23, 24), realistic clinical reactions have been seen in clinical studies where patients with various B-cell carcinomas have been managed with CD19 CAR T cells.

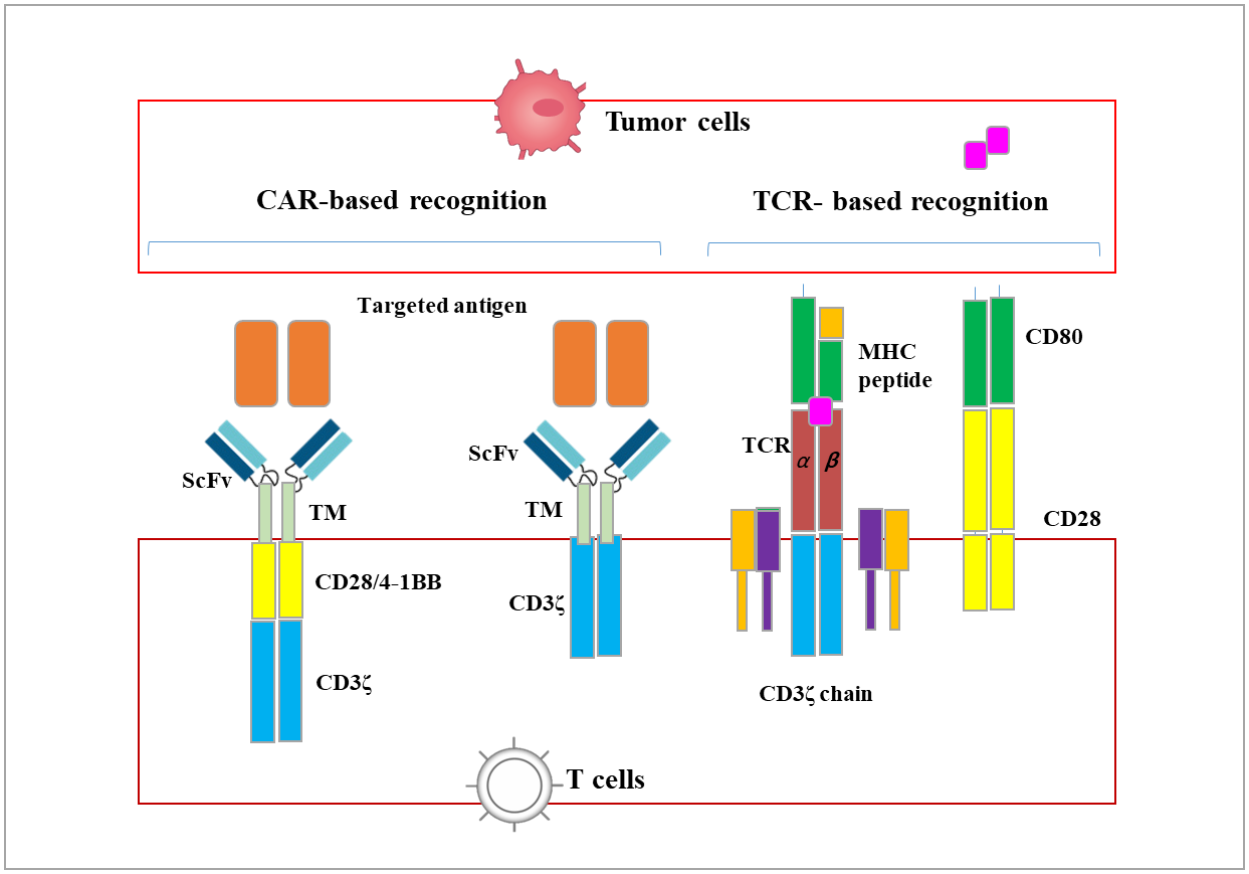

Figure 2. Components elaborate in TCR and CAR identification and activation. TCR consists of an α and a β chain, which is expressed in complex with CD3 chains. TCR detects proteins presented as peptides by MHC molecules. Stimulation of CD28 is essential for the activation and generation of interleukin-2 and other cytokines.Ttumor cells as well as antigen-presenting cells in the tumor microenvironment do not express excitatory molecules. While first-generation CARs signal only through the CD3ζ chain, second-generation CARs contain a signaling amplitude of an excitatory molecule, e.g., CD28.

Among the first hopeful findings in the context from National Cancer Institute (NCI) researchers, which released a case analysis in 2010 in which a heavily pretreated patient with follicular lymphoma experienced a dramatic partial remission (PR) after obtaining preconditioning chemotherapy obeyed by intake of T cells retrovirally transduced to describe a second-generation CD19 CAR with CD28 costimulation parts. T cells induced with a lentiviral vector transporting a CD19 CAR with a 4-1BB costimulation parts displayed remarkable antileukemia usefulness (25, 26). Two of the three treated groups with end-stage developed chronic lymphocytic leukemia (CLL) achieved complete remissions (CR), with the third achieving a limited response. The outcomes of the experiment after full enrollment were recently released, and they showed an increased frequency of 57 percent, with 4 of 14 treated patients in

CR and 4 PRs (27). Interestingly, the research found that the knowledge of CAR T cells to develop in vivo over time is associated with clinical outcomes. Moreover, CAR T cells survived and functioned for more than four years in the first two patients who achieved CR with no recurrence. Even before merged with ibrutinib, a small-molecular inhibitor of the enzyme Bruton's tyrosine kinase (BTK) correlated with greater B-cell activation and expansion, CD19 CAR T cell role and engraftment may be enhanced additional (28).

One of the most impressive reactions with CD19 redirected T cells have already been noted by organizations at UPENN, Memorial Sloan Kettering Cancer Center (MSKCC), and the National Cancer Institute (NCI) in patients with protective or recurred acute lymphoblastic leukemia (ALL), with CR rates from 70 to 90 cases in around 65 cases across the three tests (29). Whereas the therapy affected the cytogenetic and molecular treatment of her leukemia, a second BMT administered three months after the T cell injection precludes an interpretation of the UCART19 therapy's long-term effectiveness. To prevent alloreactivity, the infused allogeneic CAR-expressing T cells were gene transcribed with nucleases to interrupt the expression of the endogenous TCRs (30).

Allogeneic CAR T cells have been shown in research to not only stimulate tumorigenesis but rather to drive GVHD, and as such the UCART19 method is analytically essential for high TCR silencing effectiveness or efficient depletion of TCR expressing T cells prior to infusion. A clinical study of a multiple myeloma patient in remission after CD19 CAR T cell treatment is also noteworthy, despite the lack of noticable CD19 expression in 99.95 percent of the patient's neoplastic plasma cells (31, 32). It is theorised that the reaction is induced by that of the abolition of a small population of CD19 expressing myeloma stem cells or the elimination of CD19 expressing cells that play a major role in the maintenance of myeloma biogenesis. In patients with different chemotherapy-refractory B-cell lymphomas, inspire and motivate clinical outcomes have been acquired, such as CR in four out of seven clinically important patients with diffuse large B-cell lymphoma (DLBCL) after infusion of CD19 CAR T cells (33). In comparison, the clinical utility of CAR T cells in nonhematological, tumor cells has been hard to demonstrate. CARs targeting mesothelin, which would be upregulated in human epidermal growth factor receptor family members, a variety of solid tumors, upregulated in pancreatic, breast, non-small-cell lung cancer, bladder, neuroblastoma associated GD2, salivary gland, endometrial, and ovarian predominate among open clinical guidelines. Nevertheless, a number of targets are being studied in clinical studies, including MUC1 and carcinoembryonic antigen (CEA), which are upregulated in numerous malignancies, vascular endothelial growth factor receptor 2 (VEGFR2), which is upregulated in tumor vasculature and fibroblast activation protein (FAP), which targets cancer-associated fibroblasts in the tumor stroma (34-36).

Conclusion

Adoptive transfer of gene-modified T cells is a novel treatment method that is still in its early stages. CAR-redirected T cells are renewable medicine that can proliferate in the patient after infusion and then persist and provide develop a system immunity. Clinical efficacy with CD19 CAR T cells in leukemia and lymphoma has enhanced the field and resulted in substantial pharmaceutical and venture investment capital in the biotech segment, and also developing successful academic-industrial partnerships to investigate new findings in basic research that may translate into clinical and commercial effect.

This quickly evolving area difficulties that must be acknowledged in order to realize the promise of CAR T cell therapy for a broader use. Whereas CAR T cell treatments have shown promising preliminary efficacy in solid tumors, clinical data to date has fallen far short of expectations for game-changing cell therapy. Translational study is highly concerned with improving the specificity, usefulness, and safety of CAR T cells for use in cancers other than leukemia. Truly tumor-specific surface antigens are rare, and effective processes to mitigate life-threatening and unexpected off-target toxicities are critical. T cell therapies together with immunomodulatory agents such as checkpoint inhibitors and cytokines, as well as small-molecular antagonists which prevent biological reactions important for tumorigenesis, represent an

exciting opportunity that may have a synergic effect in augmenting antitumor reactions.Advancements in genetic manipulation , T cell choice and expansion strategies, and the development of safer and more effective viral and nonviral vectors will all help to improve T cell gene therapy integration. Finally, significant efforts are being made to develop universal and off-the-shelf, allogeneic T cell drugs in order to overcome the difficulties in dealing with complicated logistics and production of individualized T cell treatment in the autologous configuration.

Author contributions

SV and **SEN** wrote and completed the manuscript. **AAS** designed, wrote and edited the manuscript comprehensively. All authors confirmed the final version of the paper.

Conflict of interest

The authors declare that they have no conflicts of interest.

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