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Immunotherapy: The next generation of cancer treatment

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ABSTRACT

Immunotherapy is a method of cancer treatment that uses the patient's immune system to attack the tumor cells more effectively. Cancer is the second leading cause of death worldwide. Most types of cancer are treated using a combination of chemotherapy, radiation, and surgery. Recently, immunotherapy has become a standard treatment for patients with various types of cancer.

Lung cancer is one of the deadliest types of solid cancer. Recently, there has been a renewed interest in using immunotherapy to treat lung cancer after seeing positive results using immune checkpoint inhibitors. Indolent B-cell non-Hodgkin lymphoma establishes key interactions with the immune microenvironment to ensure survival and prevent antitumor immune activation. However, several immunotherapy approaches have been developed to boost these effects. The last decade witnessed several treatment options for patients with chronic lymphocytic leukemia, first-line treatment and second-line treatment after relapse.

Immunotherapy has several different types and ways of treating cancer by targeting the immune system, not the tumor itself. The adoptive T-cell transfer is a new area of transfusion medicine. Adoptive cell therapy provides an additional treatment option for patients. Immune checkpoint inhibitors have emerged as one of the most promising therapeutic options for patients in the history of cancer treatment. This group of drugs releases the brakes of the immune system. Monoclonal antibodies are being used for the treatment of various diseases. As of March 2017, the United States Food and Drug Administration (FDA) has approved approximately 60 therapeutic Monoclonal antibodies. Oncolytic virus therapy has recently been recognized as a promising new therapy. Oncolytic viruses are genetically engineered or naturally occurring viruses that selectively replicate in and kill cancer cells. Cancer vaccines are designed to promote tumor-specific immune responses and prevent or treat cancer. Immune System Modulators Drugs activate the immune system and become more powerful and able to destroy cancer cells.

Due to the development of unique therapies based on the activation of immunotherapy mechanisms against cancer growth made in recent years, we have witnessed advancements in cancer treatment options. However, most patients with advanced-stage of cancer remain with almost no treatment options.

Keywords: Adoptive Cell Therapies, Checkpoint Inhibitors, Immune System, Modulators Drugs, Monoclonal Antibodies, Tumor.

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INTRODUCTION

Immunotherapy is a rapidly advancing method of cancer treatment that has sparked the most interest in the recent decades. Immunotherapy involves types of antibodies that block immune checkpoint molecules [1], which help the body's immune system to attack cancer cells. Thus, immunotherapy is a treatment method that uses the patient's immune system to attack the tumor cells more effectively. The immune system protects the body from

infections and diseases, and includes the spleen, lymph nodes and white blood cells. In most cases, the immune system can detect and destroy abnormal cells, inhibit tumor development, and eliminate malignant cells [2].

Cancer is the second leading cause of death worldwide, most types of cancers are treated by a combination of chemotherapy, radiation, and surgery (depending on the type of cancer) [3]. Cancer growth and spread are not only dependent on tumor cell characteristics, but they are also affected by their interaction with the immune system [4]. Immunotherapy has become a standard treatment for patients with various types of cancers [2]. Immunotherapy as cancer treatment is considered an alternative modality of treatment; it aims at preventing the metastatic spread of the disease and improving the patients' quality of life [3].

The use of immunotherapy for treatment of cancer was described more than a century ago by Dr William B. Coley [4]. With the development of the immunotherapy, the focus was more on treating the specific tumor's biologic characteristics [1]. Immunotherapy needs to find ways to manipulate the immune system in patients who show little or no immune response to their cancer. Immunotherapy treatments are now approved for multiple cancer types, either as first treatment or when standard first-line treatments, such as chemotherapy, fail [1].

Lung cancer is one of the deadliest types of the solid cancers. Immunotherapy in lung cancer has become a reality, and it is now being used in clinical practice. Recently, there has been a renewed interest in lung cancer treatment using immunotherapy following positive results using immune checkpoint inhibitors to help unleash suppressed immune responses [4].

The treatment of lymphoma has advanced significantly over the past two decades with the development of multiple new immunotherapy approaches [5]. Indolent B-cell non-Hodgkin lymphoma establishes key interactions with immune microenvironment to ensure survival and prevent antitumor immune activation. However, several immunotherapy approaches have been developed to boost these effects. The availability of specific antigens and the easy accessibility of the immune system to this disease have supported the extensive study of immunotherapy treatment of B-cell lymphoma treatment [6].

Acute myeloid leukemia is the most common forms of acute leukemia in adults, it is in aggressive and devastating disease, and is rapidly progressive, with poor prognosis [7]. Immunotherapy treatment, such as bispecific antibodies, chimeric antigen receptor T cells, and immune checkpoint inhibitors, will generate meaningful disease control for this type of leukemia [7]. The combination of chemotherapy and immunotherapy treatment can show promising responses, but should be employed judiciously, cautiously, and in the right setting. For example, the chemotherapy treatment inducts functional and numeric changes in immune effector cells and may impede the collection and manufacturing of high-quality T-cell for adoptive transfer, thus consecration should be given to the optimal timing for combining the immunotherapy treatment with chemotherapy [7].

Acute lymphoblastic leukemia, which is a malignant disease that mainly affects children, is still a medical challenge, especially after relapse or for refractory cases of the disease. It is aggressive hematological disorder that results from the progressive accumulation of genomic alterations in T-cell precursors developing in the thymus. Nowadays, the use of intensive chemotherapy as the standard front-line therapy for T-ALL has raised cure rates to above 85%. Recent advancements in targeted immunotherapies for B-cell malignancies have caused unprecedented expectations for the successful treatment of acute lymphoblastic leukemia patients. Over the past few years, immunotherapy based on Immunotherapy with Monoclonal Antibodies, and adoptive transfer of T cells engineered to express CAR T Cells against tumor antigens has emerged as a powerful strategy in the treatment of refractory hematopoietic malignancies such as B-Acute lymphoblastic leukemia [8].

The last decade witnessed the development of several treatments options to be used for patients with chronic lymphocytic leukemia, for first-line treatment and second-line treatment after relapse, the vast majority of patients with relapsed or refractory chronic lymphatic leukemia carry poor prognostic, the immunotherapy treatment become as option for this patient. For example, Lenalidomide (immunomodulatory drugs) offer an overall response rate of 32%-47% in patients with relapsed and refractory disease. Using Lenalidomide as a signal agent or in combination with immunotherapy have shown promising response rate [9].

Breast cancer is a leading cause of cancer related deaths in women all over the world [10]. There is no effective therapy for patients with invasive and metastatic breast cancer.

Immunotherapy may be proved effective in treating patients with invasive and metastatic breast cancer [10]. The treatment landscape is changing with the development of immunotherapy treatment, immune checkpoint inhibitors, including programmed cell death 1 (PD-1) and programmed cell death ligand 1 (PD-L1) [11].

Antibody based immunotherapy, such as the monoclonal antibody against HER2 (Trastuzumab drug), is successfully used in the treatment of breast cancer. Also, the cancer vaccine immunotherapy is a promising method to treat breast cancer [10].

TYPES OF IMMUNOTHERAPY TREATMENTS

As mentioned early, immunotherapy treatments help our immune system to recognize, target, and kill cancer tumor cells. Different immunotherapy treatments have different way of treating cancer by targeting the immune system, not the tumor itself.

Adoptive Cell Therapies

Adoptive T-cell transfer is a new area of transfusion medicine [12]. It provides an additional treatment option for patients. The ultimate goal of adoptive cell therapy for malignant is to create an optimized personalized cellular product solely reactive to the tumor [13]. This group of treatment gives our immune cells the ability to find and kill more cancer cells after boosting their number or changing them in a laboratory [14].

Tumor-infiltrating lymphocyte therapy: In the tumor-infiltrating lymphocyte therapy, the T-cells that have started to attack the cancer cells are removed and grown in large batch in laboratory, and then the activated cell fighters are infused back to the patient's body.

Engineered T-Cell receptor therapy: This treatment gives the T-cell the ability to find cancer cells more easily. It is used by removing the T-cells from the patient's blood and reprogramming the cells in a laboratory so that it targets the surface of the cancer cells more effectively.

Chimeric antigen receptor (CAR) T-Cell therapy: The first chimeric receptor was designed in 1989 by Eshhar's group at the Weizmann Institute of Science in Israel [15]. Adoptive T-cell

therapy was developed in order to treat advanced cancer cases with patients' own T-cells. The T-cell are isolated using leukapheresis, and are harvested and genetically modified by adding receptors to the surface of the T-cell to make them powerful and turn them into special tumor cell killers, using viral and non-viral transfection methods. The T-cells are modified and expanded in cultures, when the T-cells are ready; they are transferred back to the patient [15]. CAR therapy has shown a potential paradigm shift in the treatment of refractory or relapsed cancers. The use of CAR therapy was successful the treatment of hematological cancers. Furthermore, CAR therapy for solid tumors has shown limited success so far, due to the tumor histopathological characteristics [15].

Natural killer cell therapy: The natural killer cells attack and destroy foreign invaders to the body including cancer cells. Adding CARs to the natural killer cells makes them more specifics and powerful, and more able to target cancer cells [14].

Immune Checkpoint Inhibitors

Immune checkpoint inhibitors are one of the most promising treatment options for cancer patients [16]. This group of drugs releases the brakes of the immune system. They block the proteins PD-1, PD-L1, CTLA-4 [14], and are designed to interfere with inhibitory pathways that naturally constrain T-cell reactivity, immune checkpoint inhibitors release inherent limits on the activation and maintenance of T-cell effector function [16].

Monoclonal Antibodies

Monoclonal antibodies are used for the treatment of various diseases. As of March 2017, the FDA has approved approximately 60 therapeutic Monoclonal antibodies which are currently under evaluation in various phases of clinical trials [17].

Naked monoclonal antibodies: Called "naked" because they are not attached to anything. Naked monoclonal antibodies are the most type used in the treatment of cancer. This drugs group boosts the immune system so that is responds to the cancer cells, or blocks antigens that help cancers grow and spread [14].

Conjugated monoclonal antibodies: This group of drugs is used with chemotherapy treatment or radioactive particle treatment, as it improves the performance of these drugs and helps them work better and more effectively in the elimination of cancer cells [14].

Bispecific monoclonal antibodies: This group of drugs can attach to specifics target proteins at once, which help the immune system attack cancer cells. An example is Blinatumomab, which is a drug used for the treatment of the leukemia. The drug attaches to leukemia cell protein and to the T-cell protein, as a result, the T-cell can destroy the leukemia cancer cells [14].

Oncolytic Virus Therapy

Oncolytic virus therapy has recently been recognized as a promising new therapy for cancer. This group is defined as genetically engineered or naturally occurring viruses that selectively replicate in and kill cancer cells without harming the normal tissues. T-Vec (Talimogene Laherparepvec) a second-generation oncolytic herpes simplex virus type 1 was recently approved as the first oncolytic virus drug in the USA and Europe to treat metastatic melanoma [18].

Cancer Vaccines

Cancer vaccines are designed to promote tumor specific immune responses, thus preventing or treating cancer [19].

There are four vaccines that have proved that they prevent cancer:

- Cervarix, Gardasil, and Gardasil-9: which protect from human papilloma virus, which is linked to cervix, anus, penis, throat, vagina, and vulva cancers [14].
- Hepatitis B vaccine prevents and protect against Hepatitis B [14].

Additionally, there are three FDA-approved vaccines that treat cancer:

- Sipuleucel-T (Provenge), which treats advanced prostatic cancer.
- Talimogene Laherparepvec (T-VEC), which treats melanoma skin cancer.
- Bacillus Calmette-Guerin, or BCG, which treats bladder cancer in its early stage [14].

Immune System Modulators Drugs

This type of immunotherapy treatment activates the immune system so that it becomes more powerful and is able to destroy the cancer cells.

Interleukins: The Interleukins is a type of protein the white blood cells produce during immune system response to cancer. The Interleukin IL-2 is a man-made version of the protein which can increase the number of T-cells and natural killer cells in the human body. For example, the IL-2 Aldesleukin (Proleukin) has been proved to treat advanced cases of kidney cancer and metastatic melanoma [14].

Immunomodulatory drugs: These types of drugs improved the treatment of some types of cancer. For example, Lenalidomide (Revlimid), Thalidomide (Thalomid) drugs we used for the treatment of Multiple Myeloma [14].

SUMMARY

During the past years, the advancements in understanding the nature of tumor specific immune responses encouraged researchers to develop more refined approaches to immune-mediated therapies [10].

Immunotherapy treatments have started a new era in the treatment of various types of cancers. In recent years, studies and drug usage have significantly improved their efficiency, and extended the life expectancy of cancer patients in the field of melanoma, lung cancer, Leukemia and more.

There is clear great progress in the treatment of cancer even in patients with advanced cases of cancer that are being gradually treated. Immunotherapy treatments have also improved the quality of life and extending life expectancy of patients. Furthermore, biological and immunotherapy treatments allow for personalized treatment for each cancer patient, which makes them more effective treatments.

As a result, in recent years, we have witnessed advancements in cancer treatments thanks to the development of unique therapies that are based on the activation of immunotherapy mechanisms against the cancer growth. However, despite these developments, most patients in their advanced stages of cancer are left with almost no

treatment options.

DECLARATION OF COMPETING INTEREST

Author declares no conflicts of interest.

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