Current Trends in Cancer Immunotherapy

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Abstract. Cancer is known as the second cause of death worldwide. Although various methods have been implemented such as chemotherapy, radiotherapy, and surgical resection of tumors, and have shown satisfactory results, we are experiencing an increase in the number of patients who do not benefit from these treatments. Moreover, these treatments may cause severe side effects and greatly impact the patient's quality of life. The insufficient precision and toxicity of accessible therapeutics have encouraged an increased exploration of alternative approaches to treating cancer, namely immunotherapy. Immunotherapy includes monoclonal antibodies, immune checkpoint blockades, cancer vaccines, and dendritic cell vaccines as the latest and most efficient methods in combating cancer. It also provides a place for a more molecularly targeted approach to treating cancers, using biomarkers that will ultimately achieve personalized immunotherapy. Immunotherapy has shown an immense advancement in the treatment of cancers and has the needed potential to become the first therapeutic option in treating most cancers. In this paper, we discuss prominent methods of immunotherapy in cancer treatment along with their prospective furtherance.

Keywords: Immunotherapy · Monoclonal antibodies · Cancer vaccines · Immune checkpoint blockades · Personalized immunotherapy · Dendritic cell vaccines

1 Introduction

Ever since it first became known to doctors and scientists, cancer has been a major challenge to prevail over. Several methods of treating cancer gained popularity and have shown benefits for a large scale of cancer patients. These methods include surgical resection of tumors, chemotherapy, radiotherapy. However, these measures are considered aggressive as they can cause serious side effects that may impact the patient's quality of life.

To reduce the toxic effects of traditional radiotherapy and chemotherapy, scientists started to exploit the body's own immune system to kill cancer cells. This led to the development of a new approach to treating cancer, known as immunotherapy.

Immunotherapy strengthens the body's natural immune system and allows the immune cells to identify cancer cells by recognizing specific antigens found on their

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surface. The success of immunotherapy has largely been limited by the cancer cells' capability to avoid the immune system in various ways [1].

Recently developed approaches tend to be involved in stopping the avoidance of cancer cells. Immunotherapy includes several therapies such as monoclonal antibodies, immune checkpoint blockades, cancer vaccines, and dendritic cell vaccines. The advancements in these methods have provided basis for reaching personalized immunotherapy.

Immunotherapy has a great potential of becoming the first therapeutic option when it comes to most cancers. However, similar to any other novelty, some of these treatments have serious side effects such as nausea, fever, and diarrhea [2].

This paper aims to explore the concept of cancer immunotherapy and provide a review of current trends and developments in the area of cancer immunotherapy.

2 Monoclonal Antibodies

The immune system produces antibodies that recognize malignant or pathogenic cells in the body by antigens expressed on their surface. Antibodies attach to the specific antigens and destroy foreign particles [1]. Identification of antigens on cancer cells is the most important step in selecting monoclonal antibodies. This is an extremely challenging task because cancer cells are sensitive to mutations [1].

There are several mechanisms by which monoclonal antibodies destroy cancer cells. One of the main mechanisms is referred to as targeted therapy [1, 3]. Monoclonal antibodies have the ability to recognize antigens on cancer cells and mark them as a target that the immune system will destroy. If some monoclonal antibodies are directly fused to cancer cells, it can lead to cell apoptosis [4].

Monoclonal antibodies can be divided into naked monoclonal antibodies that have a single function and can act directly on cancer cells. The second group is conjugated monoclonal antibodies that deliver radioactive particles or chemotherapy drugs directly to cancer cells. Bispecific monoclonal antibodies are the latest group of antibodies.

They consist of two antibodies that target different specific antigens.

Monoclonal antibodies can also be divided according to genetic development techniques. The first generation of monoclonal antibodies is composed of murine monoclonal antibodies that have not been able to interact with the human immune system. The next generation of chimeric monoclonal antibodies consists of constant human regions and variable mouse regions [5]. Humanized monoclonal antibodies are 95% human, and the remainder is the mouse region that determines complementarity. Finally, we arrive at fully-humanized monoclonal antibodies that are 100%, sequencelike human [6].

Monoclonal antibody-based treatment has proved to be one of the most successful treatments for hematologic malignancies and solid tumors in the last twenty years. This therapy is based on decades of research that has focused on understanding the interaction between cancer cells and immune system cells, and techniques for generating optimal antibodies at tumor target sites [7].

3 Cancer Vaccines

Cancer vaccines are a new generation of vaccines, different from the traditional prophylactic vaccines because they are in charge of attacking cells already present in the body. Two types of cancer vaccines can be specified: vaccines that prevent cancer and vaccines that treat cancer.

Preventive (prophylactic) vaccines prevent viral infections that cause cancer or contribute to cancer development. These vaccines stimulate the immune system to fight viruses before they cause an infection and are administered to healthy people before cancer develops.

Vaccines used to treat cancer work to promote the body's immune system to detect cancer-specific antigens found on the surface of cancer cells, but not healthy cells. This allows the immune system to interfere with cancer cells, stop their growth and proliferation, and ultimately kill these cells. There are several categories of cancer vaccines which include cell vaccines, peptide vaccines and genetic vaccines [1].

Making treatment vaccines that actually benefit a patient is a challenge due to several limitations. The first one is that larger tumors are hard to remove using only vaccines. This is why doctors give a cancer vaccine along with other treatments. The second limitation is the use of vaccines on the older population and people with a weakened immune system (due to other cancer treatments). They will most probably be unable to produce a strong immune response after receiving a vaccine. The third limitation is the possible malfunctioning antigen presentation that could induce tolerance to the antigens contained within the vaccine and jump-start rapid tumor progression [8]. Another thing to mention is the inability to differentiate clones of highly aggressive neoplastically transformed cells because they no longer express cancer cell-specific molecules. In these cases, cancer vaccines are of little use.

For the mentioned reasons, many researchers believe that cancer vaccines may work well for smaller tumors and cancer in its early stages [8].

4 Immune Checkpoint Blockades

Immune checkpoint blockade has been one of the most effective and significant advances in cancer immunotherapy of the past decade [9]. The condition for the formation of an immune response is the presence of molecules on certain immune cells that need to be activated or inactivated, which are called immune checkpoints [10, 11]. They have the role of either promoting or inhibiting T cell activation.

Antibodies that target checkpoint molecules, cytotoxic T lymphocyte antigen 4 (CTLA4), programmed cell death 1 (PD1), and PD1 ligand 1 (PD-L1) got attention because of their ability to use checkpoints to escape from being attacked by the immune system [12, 13]. The goal of immune checkpoint blockade is to remove inhibitory signals of T-cell activation, which enables tumor-reactive T cells to overcome regulatory mechanisms and mount an effective antitumor response.

Despite its success, response rate to immune checkpoint blockades is low in most cases [14]. This has largely to do with a lack of tumor T cell infiltration that distinguishes "cold" tumors from "hot tumors". This is why hot tumors, T-cell inflamed tumors,

can benefit from immune checkpoint blockades, but cold tumors may need a different approach [15]. Several methods of turning cold tumors into hot tumors are currently under investigation.

5 Dendritic Cell Vaccines

Dendritic cells have been proven to be the connection between innate and adaptive immune systems. The goal of dendritic cells is to process and present antigens to Tcells. It can also be stated, that dendritic cells are able to play a significant role in cancer immunotherapy. Non-targeted protein and nucleic acid-based vaccines are one of the approaches in using dendritic cells in cancer immunotherapy. Although there are different methods, the most often method is based on dendritic cells, that are ex vivo differentiated from CD14 + monocytes, isolated by leukapheresis [16]. The monocytes are cultured in the presence of macrophage-colony-stimulating factor (GMCSF) and interleukin 4. Despite the fact about gathered data, that shows tolerance and good safety profile of dendritic cell vaccines, clear therapeutic outcomes emerge in less than 15% of patients [17, 18]. The success of this type of immunotherapy depends on the ability of dendritic cells to emigrate from the injection site towards lymph nodes, and the ability to elicit cytotoxic T-cells.

6 Developing Personalized Immunotherapy

Lack of precision tends to be the main cause of why many cancer patients do not obtain an effective treatment from the immunotherapies they are receiving. Thus, with each new novelty in cancer research, precision comes to be the main objective.

Recent studies are focusing on using genomic information for a more molecularly targeted approach when it comes to cancer treatment. This is done using predictive and prognostic biomarkers in cancers that serve as a predecessor to "personalized immunotherapy" [1].

The main premise of these biomarkers is to put a halt to the use of drugs that are not beneficial to the patients and advance their treatment in terms of specificity. They aim to give patients the treatment they will most likely respond to.

One method of doing this is converting "cold" tumors, less immune responsive tumors, to "hot tumors", ones that are more responsive to immune checkpoint blockades [19]. This is done by altering the microenvironment and surrounding tissue of the cold tumor and can advance the use of immune checkpoint blockades on a larger group of patients.

Achieving precision and specificity is still a daunting challenge for scientists and oncologists but might provide a viable solution for numerous cancer patients [20].

7 Conclusion

Immunotherapy has shown great potential in combating cancer. But despite its revolutionary achievements, many cancers still do not respond to immunotherapy. This

largely depends on the strength of the body's natural immune system, but also the size and severity of neoplastically transformed cells. In conclusion, to achieve precision in cancer treatment is still a major issue, but the recent use of prognostic and predictive biomarkers in cancer treatment provides significant hope, and therefore there is a need for future research that will further develop and optimize cancer immunotherapy.

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