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The Immunotherapy in Cancer Treatment: Occurring Advancement in Using the Immune System to Combat Cancer

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ABSTRACT

The cancer-immunity cycle is characterized by various stimulatory and inhibitory factors, which together regulate the immune response and halt the extreme response that may lead to autoimmune disease. Immunotherapy of cancer has rejuvenated the field of tumor immunology and revolutionized treatment options. In the present review, we discussed the recent advances in different molecular mechanisms of cancer immunotherapy. An immunotherapy is a advanced treatment that boosts humoral and cellular immunity rather than using chemotherapy or radiation-based strategy associated with non-specific targets and toxic effects on normal cells. Immune checkpoint inhibitors and T cell-based immunotherapy have already exhibited significant effects against solid tumor and leukemia. Tumor cells that escape immune surveillance create a major obstacle to acquiring an effective immune response in cancer patients. The previous year's worldview for cancer treatment has advanced from general to more precise therapeutic approaches. Chemotherapies were first distinguished as the most reliable and brief therapy with promising outcomes in cancer patients. It is a breast cancer is the most commonly diagnosed cancer in women and is a leading cause of cause death in women worldview. Despite the available treatment options, such as surgery, chemotherapy, radiotherapy, endocrine therapy and molecular targeted therapy, breast cancer treatment remains a challenge. The FDA approvals of immunotherapeutic drugs underscore the progress made. Antibody engineering has further advanced the production of specialized and potent humanized monoclonal antibodies for clinical use.

KEYWORDS: *Cancer immunotherapy, Targeted-therapies, Immune checkpoint, Monoclonal Antibodies (mAbs), CAR-T cell therapy, Antibody Drug Conjugate (ADCs), Cytokines*

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INTRODUCTION

The immune system is made up of a complex network of interconnected mechanisms that work together to provide an adaptive immune reaction against carcinogenesis and infection while maintaining immune tolerance to self-antigens. On a cellular level, cancer is caused due to the accumulation of numerous genetic alteration that result in the breakdown of normal regulatory system. Nowadays, immunotherapy is a well-known treatment strategy for cancer that can enhance the exiting anti-tumor response so that immune cells can restrict the growth of malignant cells.[1-3]

For example, the discharge of neo-antigen from malignant tumors in the first step is recorded by the dendritic cells. The second step is known as the processing step where the release of pro-inflammatory cytokines and factors triggers the activation of effector T cells by presenting the dendritic cell mediated captured antigens to T cells.[4,5]

The therapeutic options for cancer treatment have been constantly evolving, resulting in the prolongation of life expectancy among many cancer patients. None the less, cancer is still among the leading causes of death worldwide and is considered a major public health concern. The lack of effective cancer treatments capable of overcoming the natural acquisition of tumor resistance is the main reason for high mortality among cancer patients. Conventional

therapies such as surgery, chemotherapy, radiotherapy, or hormone therapy are either not available or highly toxic for patients. The recent breakthrough in the development of new generations of cancer immunotherapies and understanding of tumor immune biology have opened a brand new era of the war against cancer. Immunotherapy aims to improve the natural immune responses directed against tumor cells with fewer off-target effects compared to the generalized chemotherapies and other agents designed to directly kill cancer cells. Figure 1 present the number of publications related to the cancer immunotherapy in the past two decades.[6-10]

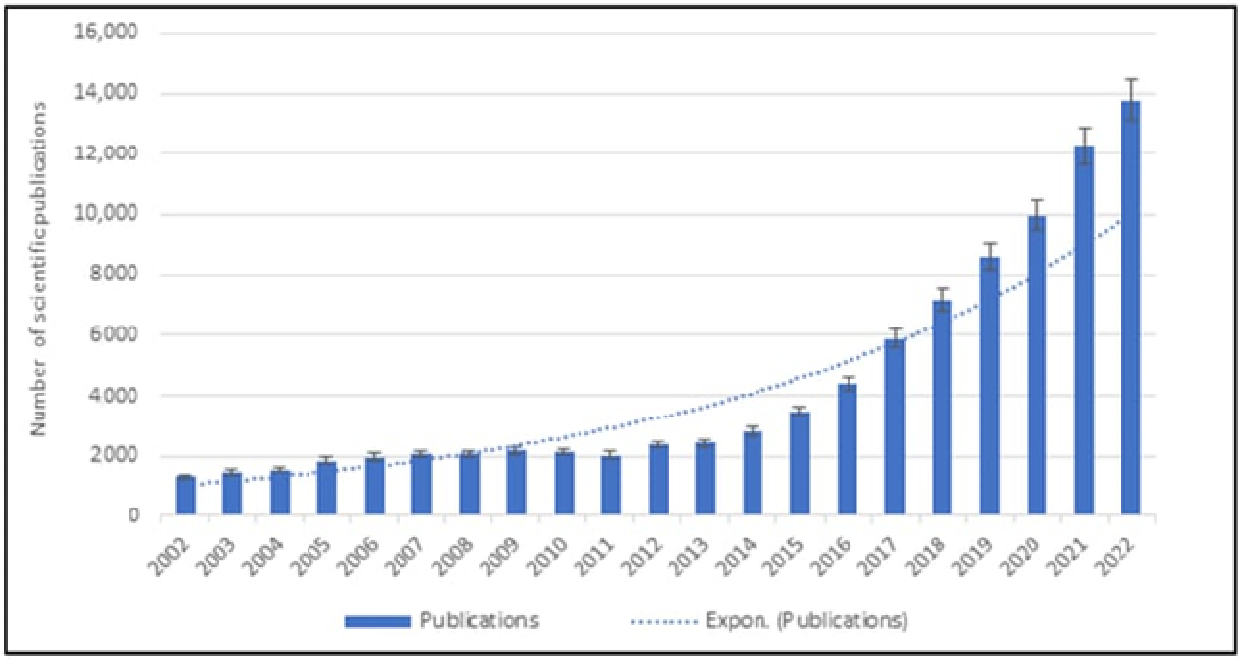

Figure 1: The number of scientific publication related to cancer immunotherapy

The immunotherapy refers to harnessing the patient own immune system to eradicate cancer. The first immunotherapy attempt was introduced in the late 19th century by two German physicians, physicians, Fehleisen and Busch, who noticed significant tumor regression after erysipelas infection. The following years, the role of immunotherapy was extensively studied by William B. Coley, also known as the "Father of Immunotherapy", who conducted experiments which involved injections of live bacteria S.pyogenes and S.marcescens into patients with inoperable bone cancers. In recent years, accumulation data support a key role for the immune system in determining both the response to standard and adjuvant therapy in patients with breast cancer.[11,12]

The immune system consists of monitoring mechanisms that detect and respond to the presence of cancer cells, a process called "immunosurveillance". Specifically, immunosurveillance consists of three phases: elimination, equilibrium and escape. During the elimination phase, the immune system cells recognize tumor-specific antigens and respond by destroying tumor cells.[13-15]

The Ehrlich first proposed the concept of the immune surveillance in 1909. It is believed that tumor cells, which often appear in the body, can be recognized by the immune system and eliminated as foreign bodies. After 50 years, Thomas proposed that the low expression of tumor cell antigen or the damage of cell immune function are the important factors of tumor development Burnet later enriched this view by developing the immune surveillance theory. It is believed that the organisms immune system can play a monitoring role and identify and eliminate any "Alien" components or mutant cells expressing neoantigens, to maintain the stability of the internal environment of the body. When the body's immune system surveillance function is low, it cannot effectively eliminate "Alien" components or mutant cells, which can lead to the development of unwanted cells and tumors.[16,17]

The cancer a complex disease that arises from the uncontrolled proliferation of anomalous cells, continues to affect millions of people worldwide. The disease is characterized by various features, including proliferative signaling, resistance to cell death and unlimited replication capability, which makes cancer cells more aggressive and promotes invasion and metastasis. Genetic mutations in cancer cells cause them to evade apoptosis and escape cell cycle control mechanisms, leading to an altered and more aggressive phenotype. Several etiologic factors contribute to the development of cancers, including physical, chemical, and biological agents that can

cause genetic mutations or DNA damage. Certain infections, lifestyle factors such as tobacco use, alcohol consumption, unhealthy dietary habits, and a sedentary lifestyle can increase the risk of developing cancer.[18]

The Neuroblastoma is a common childhood tumor that mainly affects young children, especially toddlers, and with a survival rate in high-risk patients of <50%, and it is responsible for 15% of all childhood cancer death. Neuroblastoma originates from neural crest tissue and most commonly manifests on the adrenal glands or thoracic, abdominal, or cervical paraspinal ganglia within the first few years of life. The presenting symptoms are dependent on the degree of involvement of the surrounding tissue, with two thirds of patients experiencing metastasis to the regional lymph nodes.[19-22]

IMMUNOTHERAPY

The immunotherapy is a highly innovation and sophisticated treatment approach that has emerged as a promising therapeutic option for various malignancies, including hematological and solid tumors. This therapy harnesses the patient own immune system to combat cancer, which has the potential to deliver more targeted and efficacious therapies with fewer adverse effects compared to traditional chemotherapy. Recently available immunotherapeutic strategies include immune checkpoint inhibitors, monoclonal antibodies, mRNA vaccines, and adoptive cell transfer via Chimeric Antigen Receptor T-cell therapies.[23]

The field of cancer immunotherapy has been broadly categorized into passive and active methods that correspond to the immune response elicited. Passive immunotherapy involves monoclonal antibodies to enhance the existing anti-tumor response. In contrast, active immunotherapy relies on techniques such as vaccination, non-specific immunomodulation, or targeting the immune system using antigen receptors that have been specifically designed to recognize tumor cells. Although immunotherapy has demonstrated promising outcomes, there are various impediments that limit the activation of tumor specific immune responses, such as CD8+ T-cell dysfunction, and a reduced availability of neoantigens with defect in the processing and presentation.[24]

A studies have shown that monoclonal antibodies(mAbs) can improved overall survival in cancer patients by activating various anti-cancer mechanisms, such as Antibody Dependent Cell Mediated Cytotoxicity, Complement-Dependent Cytotoxicity, promotion of apoptosis, and suppression of cell proliferation. To develop therapeutic mAbs, the hybridoma technology, established in 1975 by Kohler and Milstein, uses a fusion of immunized mouse splenocytes capable of producing antibodies with immortal cancer β-cell myeloma cells. While hybridoma technology based mAbs provide the advantages of low aggregation and high in-vivo antigen binding, they have a short half life low biological activity, and effector function onset. This statement signifies that muromonab-CD3 was the pioneering therapeutic monoclonal antibody to receive FDA approval in 1985, for use as an anti-rejection medication. The field of monoclonal antibody therapeutics has made considerable stride in recent years, with the approval of numerous mAbs to treat various cancers and other illnesses.[25]

The FDA approval chimeric mAbs, rituximab, in 1997 as an anti-cancer drug that targets CD20 for treating non-Hodgkin lymphoma. The development of Antibody Drug Conjugates (ADCs) has resulted in mAbs coupled with potent cytotoxic agents, leading to the production of new cancer drugs with improved efficacy and fewer side effect.[26]

A cancer vaccine efficacy is dependent on various factors, including the tumor microenvironment, antigen types used, vaccine formulations, and the immune composition of the tumor. Cancer vaccine can be employed either as a preventive measure or therapeutically. Initial cancer vaccine were developed as a preventative measure against viral infection linked to cancer development such as Hepatitis B. several types of cancer are associated with Human Papillomavirus (HPV) infection.

Human Papillomavirus (HPV) infection have been a public health concern, and three HPV vaccines have been approved for use since 2006. Health experts recommend individuals over the age of 11 receive the HPV vaccination to prevent HPV related illnesses. Therefore, prevention vaccines for non- viral cancers have yet to receive approval for human use. The partly due to the absence of Tumor Associated Antigens and the risk of cross reactivity induced autoimmunity on healthy tissue.[27]

In 2023, there have been several advances in the cancer vaccine research. One approach involves utilizing neoantigens, which are unique antigens present in tumor cells but not present in normal cells. By targeting neoantigens, researchers hope to develop more specific and effective cancer vaccines, which are tailored to an individual unique tumor profile. By using the patient own tumor cells to create the vaccine, the immune system can be targeted directly to attack the unique characteristics of the tumor. Success in the future of cancer vaccines

depends on transforming "cold" tumor, which lack immune cells, into "hot" tumors, which are infiltrated by immune cells capable of initiating a strong tumor specific immune response.[28-30]

The immunotherapy can fall into both different types (Figure 2), one being active immunotherapy and the other being passive. Active immunotherapy relies on the directly attacking cancer cells through the stimulation of the immune system. Passive immunotherapy utilizes the acceptance of an organisms immune system of antibodies, cytokines, and transformed immune cells to act tumor cells. Immunotherapy treatments that can target neuroblastoma cells have been in development over the course of current decades.[31,32]

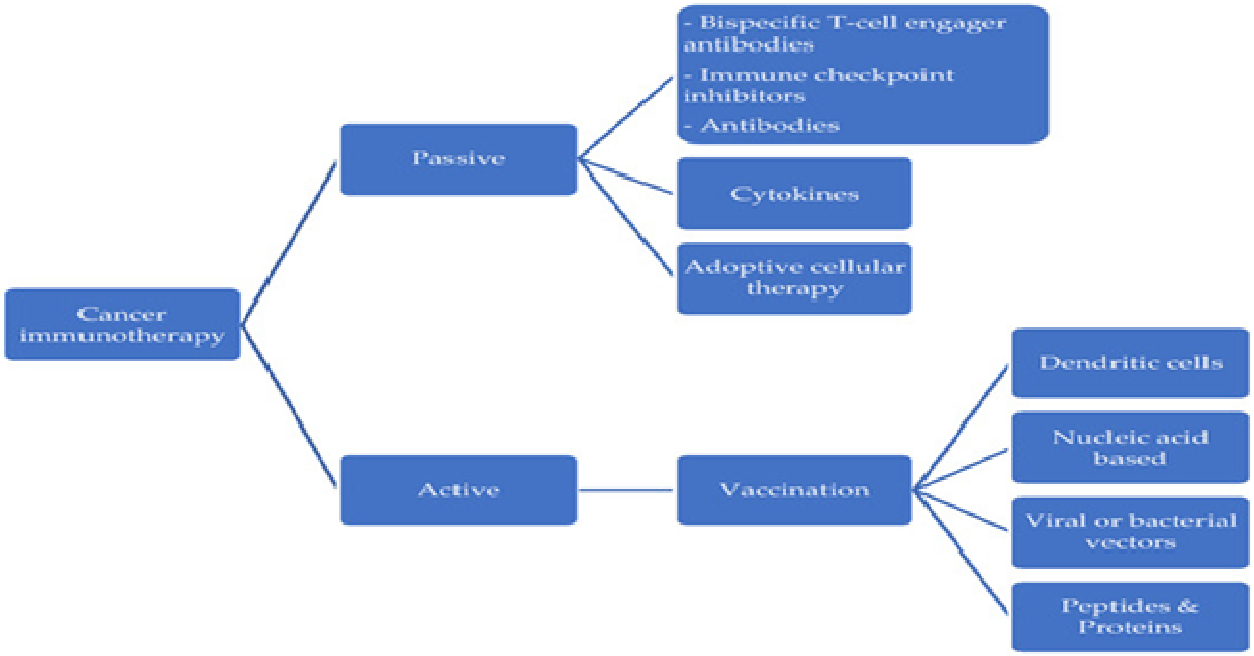

Figure 2: Classification of immunotherapies as either active or passive. In order to combat cancer cells, active immunotherapy stimulates the immune system of the cancer patient.

CANCER AND IMMUNOTHERAPY

➢ Monoclonal Antibody Immunotherapy[33,34]

According to the National Institute of Health, Monoclonal antibodies are artificially made proteins that can recognize specific targets and are widely used as a targeted cancer therapy. Most often, there categorized into those targeting immune molecules, otherwise known as immune checkpoint inhibitors, or into those targeting oncogenic membrane receptors. Figure 3 the demonstrates the two types of monoclonal antibodies in this review.

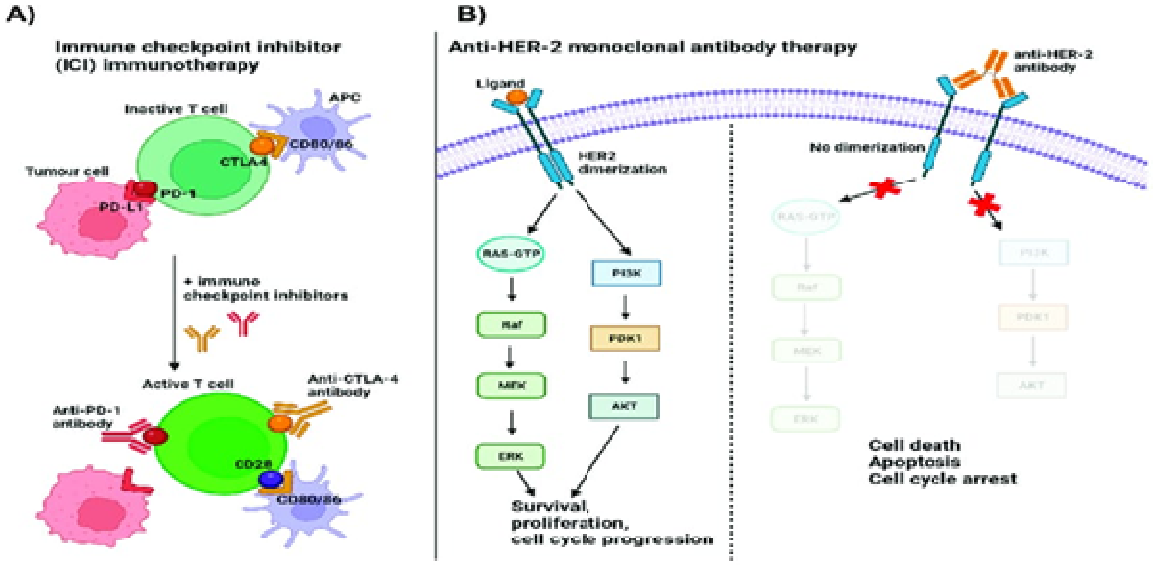

Figure 3: Monoclonal antibody immunotherapies. (A) Demonstrates the mechanism of action of anti-PD-1 and anti-CTLA-4 immune checkpoint inhibitors. (B) the mechanism of action anti-HER-2 monoclonal antibody by prevention dimerization of HER subunit.

➢ Immune Checkpoint Inhibitors[35,36]

A cancer therapy by the regulation of immune checkpoints is an approach that aims to activate the immune system against cancer cells by targeting proteins that act as negative regulation of immune responses. Cancer cells an evade immune surveillance by expressing multiple immune-checkpoint proteins, such as programmed cell death ligand 1 (PD-L1), CD80/86, and Ga19, which inhibit T-cell activation and proliferation. Therapies that target these immune-checkpoint proteins, such as immune-checkpoint inhibitors, have shown remarkable success in the treatment of various types of cancer. These drugs block the interaction between immune checkpoint proteins and their ligands, thereby releasing the inhibition of T-cell function.

➢ Cancer Vaccines[37,38]

The tumor cell lysate, dendritic cells, and nucleic acid are example of cancer vaccines. Dendritic vaccines are the most extensively researched cell-based vaccines. Autologous dendritic cell are collected from patients and engineered so that they express tumor-associated antigen, activating T cells to attached the tumor. Sipuleucel-T is one of the approved dendritic cell vaccines for the treatment of prostate cancer that was approved in 2010 for it is ability to successfully prolong patient survival. Manipulation dendritic cells to express targeted antigens and induce T cells against tumor can improve the efficacy and potency of dendritic vaccines.

➢ Adoptive Cell Transfer[39,40]

Adoptive cell transfer is a cancer treatment method that involves injection immune cells, such as T-cells, into a patient's body, they seek out and destroy cancer cells. Before being administered to a patient, T cells are usually modified or enhanced in a very successful form of ACT that involved engineering T cells to express chimeric antigen receptors (CARs) that can recognize and adhere to specific protein on the surface of cancer cells. (Figure 4).

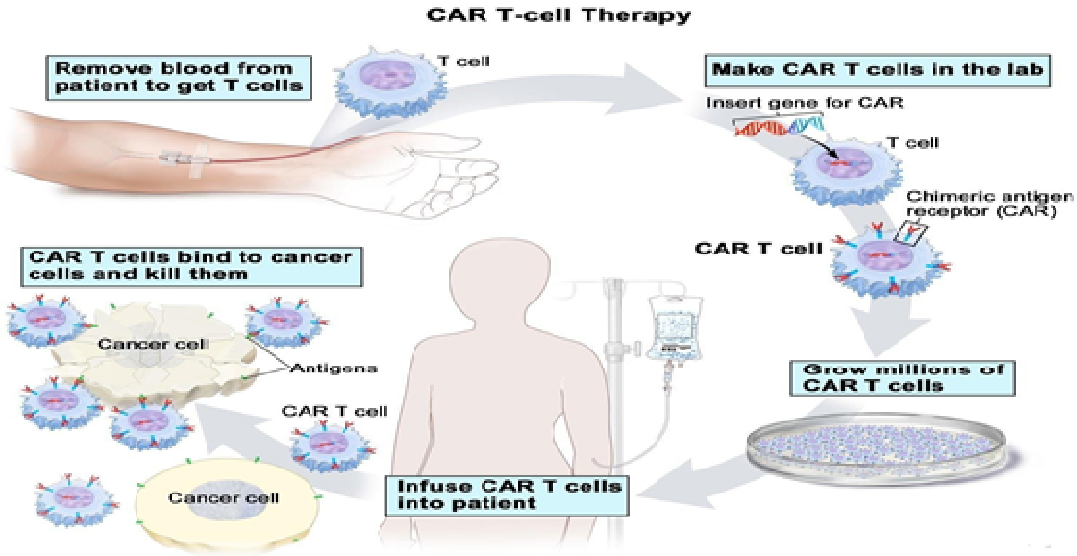

Figure 4: The CAR T-cell Therapy

➢ Cytokine Therapies[41,42]

The cytokines are chemical messengers secreted by immune and non-immune cells in reaction to cellular stresses such as bacterial infections, inflammation, and tumorigenesis to control cellular interactions. The first use of cytokines in cancer treatment occurred in 1976, following the discovery of interleukin-2 (IL-2), initially known as a T-cell growth factor, which appeared to have the capacity to activate T-cells and the exert immune-stimulatory properties. In-vitro incubation of inactive lymphoid cells, with recombinant IL-2 results in the production of lymphokine-activated killer (LAK) cells, which are cells that are capable to lyse tumor cells. The administration of LAKs and large doses of IL-2 in patients with various types of cancer have been reported to cause cancer regressions and significantly enhance antitumor response in a preclinical studies and clinical trials.

CONCLUSION

In conclusion, immunotherapy was developed in response to the ever-increasing research on cancer and understanding and the use of technologies to find an effective treatment for cancer. Immunotherapy has yielded promising results in the treatment of certain high-risk cancer. In neuroblastoma, the low immunogenicity of these tumors combined with the relatively immature immune system makes it challenging to effectively administer treatments with high levels of efficacy.

The immunotherapy has revolutionized the treatment of breast cancer, significantly improving the curative effect when added to standard therapies. Despite challenges, immunotherapy remains a promising therapeutic strategy and ongoing trials will confirm its clinical benefit in combination with conventional therapies.

The past two decades have witnessed a significant understanding of the role of the immune system in control of malignancies as well as methods employed by cancer cells to avoid immunosurveillance. Cancer immunotherapy has shown remarkable success in treating various types of cancer, including melanoma, lung cancer, and bladder cancer, and certain types of leukemia and lymphoma. Many types of cancer immunotherapy have been developed including immune-checkpoint inhibitor, cancer vaccines, monoclonal antibody, cytokines, and adoptive cell transfer technology, with significant clinical improvements in patient survival and quality of life. It's has revolutionized cancer treatment and has the potential to provide long-term remission or even cure in some cases.

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