Exploring the Impact of Immunotherapy on Cancer Recurrence

Amruta Dadasaheb Kalunkhe[1], Dr. VAishali Pardeshi[2], Dr. Sonia Singh[3], Dr. Ganesh Andhale[4], Dr. Madhuri Shelar[5]
Alard College of Pharmacy, Pune-411057, Maharashtra, India.

***Abstract*—The body's inherent defenses against cancer were known long before the modern era, as evidenced by numerous anecdotal accounts of tumors magically vanishing, sometimes on their own or following an infectious or feverish event. It is now widely acknowledged that immunosuppression is linked to an increased risk of cancer, and spontaneous tumor regression of untreated malignant tumors is a rare but well-accepted phenomena.Biologic modifiers, such as cytokines and vaccines, adoptive cell therapies, oncolytic viruses, and antibodies against immune checkpoint inhibitors, such as the co-inhibitory T-cell receptor PD-1 and one of its ligands, programmed death-ligand 1, are among the various forms of cancer immunotherapies covered here.(1) As a result of the tremendous advancements in cancer research over the years, immunotherapy has become a significant cancer therapies. Immunotherapy has shown promising results and presents a practical approach to significantly increase the overall survival rate of cancer patients while also improving their quality of life. This systematic review's goal was to evaluate immunotherapy's effectiveness in treating cancer.**

***Index Terms*—Active immunotherapy, passive Immunotherapy, Adaptive cell therapy, cancer immunotherapy, cancer vaccines.**

I. INTRODUCTION

With its quick development, cancer immunotherapy (CI) is currently regarded as the "fifth pillar" of cancer treatment, following radiation, cytotoxic chemotherapy, surgery, and targeted therapy. Antibodies targeting inhibitory immunological checkpoint molecules are the CI that has generated the most interest. It is hard not to be enthusiastic about their potential, even if they have only shown remarkable effects in a small percentage of certain cancers thus far of the several cancer kinds, breast cancer is the most often diagnosed cancer globally (2 million cases), with lung, colorectum, prostate, skin (non-melanoma), and stomach cancer following in order of prevalence [1]. Furthermore, it has been projected that the number of senior people will rise dramatically worldwide, creating a cohort of elderly individuals who are more susceptible to cancer as a result of age-related health decline [2]. By reducing or stopping the proliferation of cancer cells, a treatment plan aims to both cure the disease and increase the patient's lifespan. Nevertheless, the course of treatment for cancer may differ based on whether it is detected early or late, which will establish whether or not it has spread [3].

Immunotherapy, in contrast to traditional cancer treatments, uses the body's immune system to identify and combat cancer cells, providing a natural means of halting the disease's growth.Although the majority of cancer treatments, including surgery, radiation, and chemotherapy, have proven successful in treating primary tumors, recurrence of the disease is still a common problem because of tumor metastases or residual malignant cells [4]. As a result, immunotherapy is one of the supplementary or alternative methods that uses cancer vaccines, chimeric antigen receptor (CAR) T-cell therapy, and immune checkpoint inhibitors to treat cancer.

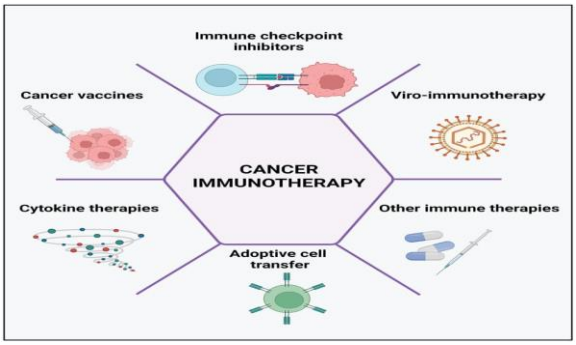
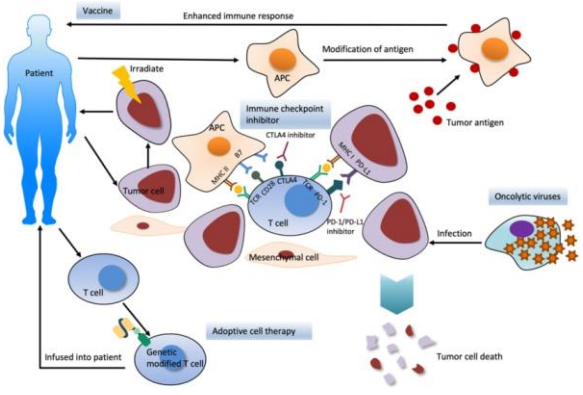


Diagram: Types of cancer immunotherapy include adoptive cell transfer, cytokines, viruses, immune-checkpoint inhibitors, and cancer vaccines.

Both passive and aggressive cancer immunotherapies are possible [5]. The foundation of passive therapy is the adoptive transfer of immune cells, tumor-specific antibodies, or immunomodulators (such as cytokines) [6]. The patient is subsequently given these materials, or cells, to start the anticancer effect. Chronic infusion-based treatment is necessary since this therapy typically does not produce immunologic memory[7].For the treatment of leukemia, renal cell carcinoma, breast cancer, melanoma, and other solid and hematologic cancers, a number of passive immunotherapies have received approval[8].Conversely, active immunotherapy uses the body's own immune cells to boost the patient's immune system in order to promote an antigen-specific antitumor impact[7].Furthermore, the goal of active immunotherapy is to produce a long-lasting antitumor response that can guard against tumor recurrence and minimal residual disease[9].The two categories of immunotherapy are nonspecific and specific. Nonspecific immunotherapy is the use of cells or chemicals that are not directed against a particular antigen. One nonspecific cellular immunotherapy that is presently being researched for the treatment of malignancies such melanoma, renal cell carcinoma, and non-Hodgkin's lymphoma is lymphokine activated killer (LAK) cell therapy [10].



Diagrammatic representation of immunotherapy:Immunotherapy techniques include oncolytic viruses, vaccinations, adoptive T cell treatment, and immune checkpoint inhibitors.

Types of Immunotherapies

Adoptive cell therapy (ACT)

The main idea behind ACT is that T cells are essential for destroying cancer cells, therefore transferring more T cells can increase anti-tumor immunity [11]. A potent and potentially curative treatment for a number of cancers is adoptive cell therapy (ACT), which uses either tumor-infiltrating lymphocyte (TIL)-derived T cells or T cells that have been genetically modified to produce tumor-recognizing receptors [12].

Adoptive cell therapy types

Therapy with tumor-infiltrating lymphocytes (unmodified cells).

Modified cells used in engineered T-cell receptor treatment.

T-cell treatment using chimeric antigen receptors (modified cells).

Immune checkpoint inhibitors

The immune system's normal components are called immunological checkpoints. Antigen presentation, in conjunction with several co-stimulatory and co-inhibitory cues, determines T-cell activation functionally. These co-inhibitory signals will cause the stimulatory signal to fail, which will decrease the immune response by failing to trigger cytotoxicity and causing T-cell anergy or death [13,14]. Checkpoints are co-inhibitory molecules that maintain immunological tolerance under normal physiological settings and avoid an overreaction.Immunocheckpoint inhibitors most commonly target three molecules:

PD1 (programmed cell death receptor 1)

CTLA4 (cytotoxic T lymphocyte-associated molecule 4)

PD1 (programmed cell death ligand 1)

Currently, there are two main kinds of checkpoint inhibitors in use: anti-CTLA-4 antibodies (like Ipilimumab) and anti-PD-1 antibodies (like Nivolumab and Pembrolizumab) [15].

Targeted monoclonal antibodies

MoAbs are a type of active immunity in which they target a particular antigen found on cancer cells. MoAbs can be coupled with therapeutic medications that would cause cancer cells to be cytotoxic, or they can be unconjugated [16].

Oncolytic virus therapy

The discovery that virus-infected tumor cells are destroyed by the cytopathic effects of viruses led to the development of oncolytic virus therapy.Viruses are infectious agents that may enter live cells and take control of their genetic machinery, enabling the virus

to multiply within the cell.This treatment involves infecting tumor cells using genetically engineered viruses. The cytopathic effects of viruses boost systemic antitumor immunity by inducing a pro-inflammatory milieu that destroys virus-infected tumor cell [17,18]. In 2015, the US Food and Drug Administration (FDA) authorized talimogene laherparepvec (T-VEC), the first oncolytic virus therapy, to treat melanoma. The genetically modified herpes simplex virus T-Vec, sometimes referred to as Imlygic, has been licensed for the treatment of incurable metastatic melanoma and shows remarkable clinical improvements for patients with advanced melanoma.

II. CANCER VACCINES

As with the use of monoclonal antibodies, cancer vaccines likely form one of the most varied families of immunotherapeutic methods. There are two categories of cancer vaccine development: therapeutic and preventative, commonly known as prophylactic.For over 30 years, preventative cancer vaccinations have been used with varying degrees of success to stop the elevated risk of carcinogenesis brought on by different viral infections. Hepatitis B virus (HBV), human papilloma virus (HPV), Epstein-Barr virus (EBV), human immunodeficiency virus type-1 (HIV-1), hepatitis C virus (HCV), and Kaposi's sarcoma-associated herpes virus (KSHV) are the six human viruses currently known to be carcinogenic to humans [19].

The first of these preventative cancer vaccines was the HBV vaccine, which was authorized by the FDA in 1981 and has been a normal component of newborns scheduled routine vaccinations ever since [20]. In addition to significantly lowering HBV infection rates, widespread use of the vaccine also decreased the risk of hepatocellular carcinoma (HCC), with vaccinated persons continuing to benefit from the vaccine's vaccination even as they aged [21].

The human papillomavirus vaccination is the second cancer prevention vaccine. Harald zur Hausen showed in the 1980s that the majority of cervical cancer biopsies and cell lines produced from cervical cancer contained two strains of HPV, HPV16 and HPV18[22]. Instead of attempting to stop cancer from developing, therapeutic cancer vaccines seek to increase the immune system's response to an already-existing cancer. The discovery that cancer patients can, in fact, create helper T cells and cytotoxic T cells that are specific to antigens expressed in their tumors led to the development of this strategy [23]. There are various methods used to create therapeutic cancer vaccines, which aim to activate or strengthen these innate T cell responses against the tumor cells [24].

Peptide or protein-based vaccines

These cancer vaccines employ a full protein or brief peptide extracted from the tumor cells as the immunization's tumor cell-specific antigen. This form of vaccination, known as Vitespen, is peptide-based and uses the glycoprotein (gp) 96-peptide complex (HSPPC-96), an autologous tumor-derived heat shock (chaperone) protein, as an antigen. Gp100 (or Gp100-based) is another peptide-based therapeutic cancer vaccine that uses peptides from the glycoprotein 100 as a melanoma-associated antigen.

Autologous or allogeneic whole-tumour-cell vaccines

Allogeneic or autologous tumor cell lines are used to create whole-tumor-cell cancer vaccines. The idea that this type of vaccine would not elicit an effective anti-cancer immune response because it was not pre-existing in the first place has led to the abandonment of this approach, despite the fact that the use of autologous tumor cells eliminates the antigen selection problem by offering the benefit of targeting the individual's own tumor associated antigens [25]. However, because it can introduce many antigens and so improve the immune response, the use of allogeneic tumor cell lines for the whole-tumor-cell vaccination was preferred. Using Allogeneic Prostate Cancer Cell Lines VITAL-1 and VITAL-2 that are engineered to secrete GM-CSF, GVAX is an example of this type of cancer vaccines [26].

III. GENE THERAPY-BASED VACCINES

Since gene therapy-based vaccines employ viruses to introduce the vaccine, they are also known as vector or viral-vector vaccines. The goal of this strategy is to stimulate and improve the immune responses against cancer cells that carry the specific antigens by engineering these viral vectors to encode for those antigens.The poxvirus family of viruses makes an appealing choice for this treatment because of their safe utilization since the 1960s, even if the benefits of using viruses as a delivery vehicle include facile gene

insertion, low cost, and the capacity to elicit a lasting immune response[27].

Idiotype immunoglobulin-based vaccines

These cancer vaccines are made by combining a patient's malignant B lymphoma cells with a myeloma cell line. The resulting heterohybridoma produces antibodies that contain idiotypes, which are antigens unique to the patient's tumor (25). In order to improve their immunogenic qualities by eliciting certain T-cell responses, the idiotypes are then separated from the antibodies generated by these heterohybridoma B cells, purified, and attached to keyhole limpet hemocyanin (KLH)[28]. The BiovaxID vaccine was created as a cancer vaccination that protects against B-cell lymphomas.

IV. DENDRITIC-CELL-BASED VACCINES

Dendritic-dell-based vaccines may provide the most promise for therapeutic vaccination, which is still an area that requires further research, out of all the cancer vaccines covered here. Given their strong T-cell activation and consequently long-lasting anti-cancer immune response, dendritic cells are now recognized for their significance. One of the dendritic-dell-based vaccines is DCVAX-Prostate, an autologous dendritic cell vaccine; however, unlike peptide or protein-based vaccinations, it does not use a complete protein and does not administer GM-CSF [29].

Sipuleucel-T (Provenge)

The patient's own peripheral blood mononuclear cells are used to create this autologous customized vaccination. The remaining dendritic cells, T cells, B cells, and natural killer cells are incubated for 36 to 44 hours ex vivo with a fusion protein PA2024, which is made up of a prostate cancer antigen, prostatic acid phosphates (PAP), and GM-CSF [30], following the leukapheresis process that eliminates platelets, monocytes, low-density lymphocytes, and erythrocytes.

Discussion

According to the current study's findings, immunotherapy, either by itself or in conjunction with traditional cancer treatments, has a great deal of promise for raising cancer patients' overall survival and progression-free survival rates, particularly for those whose first-line therapy has failed and their disease has returned.When immune checkpoint inhibitors were used, patients with high tumor cell PD-L1 expression, particularly those with non-small cell lung cancer, demonstrated a comparatively better response and survival rates[31].

Furthermore, studies' overall findings have improved due to cancer vaccinations. All things considered, the primary function of these cancer vaccines is to boost immune responses, which prevents the disease process from reoccurring or acts as a preventative measure against cancer brought on by infections.Patients with recurrences who have not responded to first-line therapy have been treated with immunotherapy employing dendritic cell (DC)-based immunization. Further chemotherapy treatment for sarcoma patients would be insufficient because of the tumors' resistance to the treatment and the increased risk of multiorgan failure.

Finally, although studies based on CAR T-cell treatment were less successful than the other two, they nevertheless had an impact on the overall survival rate. CAR T-cells have demonstrated some promising outcomes, particularly in clinical trials for CD19-positive malignancies, as tumors are frequently resistant to conventional treatment [32].

List of Abbreviation: Not Applicable

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