The Use of Immunotherapy to Treat Melanoma
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Cancer is a disease in which abnormal cells divide uncontrollably, often having the ability to spread to other tissues in the body. The immune system is a complex network of white blood cells, organs, and proteins that work together to fight off pathogens that enter the body. When cancer develops, the immune system should recognize and eliminate the cancer cells. However, cancer has adapted to evade the immune system. One of the ways is to express PD-L1 or CTLA-4 to activate the immune checkpoints that downregulate T-cell activity and the anti-tumor immune response[2]. Cancer can also produce a protein called ZEB1 to limit T cell infiltration in the tumor[5]. Immunotherapy is characterized by the use of different techniques to boost or restore the immune system's ability to combat pathogens[1]. When deciding on a cancer treatment, immunotherapy is an attractive option as it can help the immune system overcome the tumor's evading mechanism. In this review, we will explore melanoma and discuss the role of immunotherapy in its treatment through monoclonal antibodies and combination therapies.

Melanoma is aggressive, making it the most dangerous form of skin cancer and a great risk to health as the incidence of cases has increased steadily[3]. This cancer results from a mutation in melanocytes, which are melanin-producing cells found on the skin, inner ear, uvea, heart, hair follicles, and mucosal tissue[2]. Based on the original location of the tumor, melanoma can be characterized as either cutaneous (on the skin) or non-cutaneous[2]. Cutaneous melanoma makes up the majority (91.2%) of melanoma cases and often has a better prognosis compared to non-cutaneous[2]. Non-cutaneous melanoma, consisting of less than 10% of all cases, often has a poorer prognosis due to late diagnosis[2]. UV exposure is the biggest factor that promotes melanogenesis as it causes random mutations in melanocytes which transforms them into cancer cells[2]. This puts the fair-skinned population at a higher risk for melanoma as they have less melanin to protect against UV rays. The most common mutation, found in 40%-50% of all cutaneous melanoma patients, is the *BRAF* mutation which activates the MAP kinase/ERK pathway, affecting gene expression in the nucleus and leading to cell proliferation[3]. Patients with cutaneous melanoma usually show symptoms of having a large asymmetric lesion that may ulcerate, bleed, itch, or form additional smaller lesions nearby[3]. On the other hand, patients with non-cutaneous or metastatic melanoma present symptoms relating to organ function[3]. While melanoma is not common and is diagnosed in only 1% of skin cancers, it is the most dangerous as it contributes to 90% of all skin cancer deaths[2]. The aggressive nature of melanoma makes it crucial to diagnose in its early stages when it is relatively easy to treat with a 5-year survival rate of 97%[3]. However, after stage IV melanoma, the treatment is often very difficult with a 5-year survival rate of only 25%[2]. Once diagnosed, the primary treatment is a local wide excision surgery where the tumor is removed to gain control and prevent the further spread of cancer[2]. Following surgery, conventional therapies include radiation, chemotherapy, and targeted therapy[2]. However, in recent years, scientists have gained a better understanding of melanoma's evasion mechanisms and its progression which has led to the development of modern immunotherapies such as immune-checkpoint inhibitors, adoptive T cell therapy, and T-VEC[2]. Since then, numerous studies have been conducted to test the efficiency and effectiveness of immunotherapies and it has shown great promise in increasing the response rate and overall survival of melanoma patients.

In the treatment of melanoma and its evasion of the immune system, immunotherapy has faced significant breakthroughs as well as obstacles. To grow and advance, melanoma cells

adopt mechanisms to evade the immune system. Melanoma does this by taking advantage of the immune checkpoints to cause T cell dysfunction[2]. Immune checkpoints are pathways that act as regulators by preventing autoimmunity and reducing unintended harm to healthy cells[2]. The programmed death protein 1 (PD-1) and its ligand, programmed death ligand 1 (PD-L1) are immune checkpoint proteins that are responsible for downregulating T cell function[2]. In addition to PD-L1, other immune checkpoints are also responsible for inhibiting T cell activation such as Cytotoxic T Lymphocyte Antigen-4 (CTLA-4)[2]. Melanoma can escape from the anti-tumor immune response by producing PD-L1 or CTLA-4 on its surface to promote a regulatory response that suppresses the CD8 T cells[2]. Therefore, the blockage of these immune checkpoints can restore the antitumor immune response[2]. This led to several FDA-approved immune checkpoint inhibitor drugs including anti-PD-1/PD-L1 antibodies such as nivolumab and pembrolizumab, and anti-CTLA-4 antibodies such as ipilimumab. The introduction of these drugs showed a significant improvement in the treatment and lifespan of people with advanced melanoma. Before the introduction of immune checkpoint inhibitors (ICI), the average life expectancy for a patient with metastatic melanoma was six to twelve months. However, with ICI, it increased drastically to an overall 3-year survival rate of 50%[4]. Despite these successes, around 60% of patients either do not respond or obtain resistance to ICI treatment[5]. There are several reasons why a patient may not respond to ICI, including the tumor's limitation of T cell infiltration[5]. A research trial using human melanoma samples and melanoma mouse models showed that melanoma can escape the immune system and immunotherapy through the expression of a transcription factor called Zing Finger E-Box Binding Homeobox (ZEB1)[5]. The researchers found that ZEB1 stops the secretion of chemokines, (such as CXCL10), that attract T cells which led to the discovery that higher expression of ZEB1 in melanoma cells is linked to fewer CD8+ T cells in the tumor[5]. The lack of CD8+ T cells in the tumor makes immune checkpoint inhibitors ineffective as they depend on high T cell infiltration[5]. Due to this and other immune evasion mechanisms, ICI as a monotherapy is often insufficient and not used[4]. Thus, ICI is commonly used with other treatments such as chemotherapy and targeted therapy to increase the effectiveness of immunotherapy[4].

Recent clinical trials test new combination therapies in hopes of finding an effective treatment for melanoma. Following the successes of combining nivolumab and ipilimumab, scientists began exploring new immune checkpoint inhibitor combinations. An ongoing phase 2/3 clinical trial aims to test the efficiency of utilizing nivolumab with relatlimab compared to nivolumab alone on patients with previously untreated metastatic or unresectable melanoma[6]. To be eligible to participate in the trial, an individual needs to have stage III or IV melanoma with no prior systemic treatment for cancer[6]. Additionally, they must also consent to provide tumor tissue for biomarker analyses[6]. They must also be twelve years or older to participate[6]. Individuals will not be eligible to participate in this trial if they have an active brain metastasis, leptomeningeal metastasis, uveal melanoma, or an autoimmune disease[6]. The patients will be divided into two experiment groups, one receiving nivolumab monotherapy and the other receiving the combination of nivolumab plus relatlimab[6]. Nivolumab is a PD-1 monoclonal antibody that enforces an anti-tumor response by blocking PD-1 on T cells[2]. Relatlimab is an inhibitor of the lymphocyte-activation gene 3 (LAG-3) which is found on activated CD4+ and CD8+ lymphocytes[7]. When LAG-3 binds to MHC-II, it results in downregulation of T cell proliferation and function leading to melanoma immune evasion[7]. Because LAG-3 positive T cells are found within melanoma, scientists hypothesized that the inhibition of the LAG-3/MHC II pathway would cause an improvement of the immune response and destruction of melanoma[7].

The results of this trial were successful and demonstrated that the combination therapy proved to have a much longer progression-free survival of 10.12 months compared to 4.63 months on monotherapy[6]. These promising results led to the approval of this combination therapy by the FDA and provide hope for current and future cases of melanoma patients. Another recently completed phase 2 trial tested a new combination therapy using talimogene laherparepvec (T-VEC) and pembrolizumab[8]. This trial's goal was to find a treatment for patients whose melanoma did not respond after anti-PD-1 therapy[8]. The study consisted of 72 enrolled patients with stage IIIB to IVM1d melanoma who have had prior treatment using a PD-1 inhibitor[8]. No patients with an autoimmune disease or more than one line of anti-PD-1 therapy were accepted into this trial[8]. This study combined T-VEC, an oncolytic virus that attacks cancer cells and produces a protein (GM-CSF) that stimulates the immune system, and an anti-PD-1 drug (Pembrolizumab)[9]. The participants in the trial were divided into 4 groups; primary (group 1) or acquired (group 2) resistance to anti-PD-1 therapy in a recurrent or metastatic setting and patients who received anti-PD-1 therapy after surgery and were disease-free for less than 6 months (group 3) or 6 months/longer (group 4) before relapse[8]. After the completion of the trial, groups 3 and 4 had the highest response rates of 40% and 46.7%, which suggests that this combination therapy may become beneficial for patients whose cancer progressed after the use of anti-PD-1 in an adjuvant setting prompting further research[9]. These recent/ongoing clinical trials address the need for improved treatments and therapies for melanoma by investigating new combination therapies. Although checkpoint inhibitors have been revolutionary, many patients do not experience any benefits due to developed resistance and evasive mechanisms. By combining checkpoint inhibitors with other drugs/therapies, researchers hope to increase overall survival and prolong progression-free and disease-free survival.

Melanoma is a skin cancer that originates from a mutation in melanocytes. The invention of immunotherapy has significantly improved melanoma patient outcomes. However, despite these innovations, the response to the treatment varies with a portion of patients not experiencing any benefits. One of the main challenges researchers face is patients obtaining primary or acquired resistance to immunotherapy. Currently, scientists are working to provide new combination treatments for melanoma to overcome resistance and improve the response rate as well as long-term efficacy. Continued research and advances will be the key to opening the potential of immunotherapy, ensuring better outcomes for patients worldwide.

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