Immunotherapy in Cutaneous Melanoma

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Introduction

Cancer is a large class of diseases characterized by uncontrolled cell growth. The immune system is our body's mechanism to protect itself from alien threats, including cancer. The immune system should be able to kill cancer; however, cancer often avoids this either by preventing the activation of the immune system or avoiding detection. Immunotherapy is a method of treating cancer that relies on stimulating the immune system so it is able to kill the cancer. Immunotherapy is a common therapy to overcome cancer immune evasion because it is very effective and has relatively low side effects. In this review, we will research the causes, treatments, and the use and future of immunotherapy in Cutaneous Melanoma (CM).

What is CM?

CM is the deadliest type of skin cancer. It often comes in the form of a mole caused by exposure to ultraviolet radiation from intense sunlight. It is most common with people with light skin who live in areas that receive high levels of intermittent solar exposure, unlike other forms of skin cancer which are caused by long term UV exposure (Leonardi 2018). UV Radiation has been studied to have a negligible correlation with melanoma in people of color due to the increased photoprotection that dark skin provides against UV radiation, especially in the tropics (Lopes 2021). Additionally, studies show that women are more likely to develop CM; however, women also have a higher rate of survival (Behbahani 2020). In studies in South Africa, 10 times more white people than black people developed CM (Norval 2017). A majority of people in eastern Asia who develop cutaneous melanoma develop types that are more sun independent like acral lentiginous melanoma and mucosal melanoma, which make up a much lower percentage of cutaneous melanoma in places that receive more sunlight, like the US (Chang 2013). However, UV radiation is not the only cause for CM. Studies show that mutations in *CDKN2A* increase risk factors to develop CM. Other mutations include an 80% rate of mutation in the oncogene *BRAF* and the tumor suppressor genes *PTEN*, *NF1*, and *TP53* (Leonardi 2018). CM is different from other types of skin cancers like BCC and SCC because it has a much higher rate of metastasis leading to it being more volatile, and therefore dangerous. CM has an overall 5-year survival rate of 95%; however, due to its ability to metastasize, the 5-year survival rate can plummet to as low as 5% (Cummins 2006). Luckily, CM is easy to identify early due to the signature moles and lesions, which results in earlier treatment and curing. Before metastasis, it is often treated with surgical excision, and would be treated with chemotherapy otherwise. However, the recent approval of targeted therapies like RAF and MEK kinase have made treatment much easier by preventing angiogenesis anti-apoptosis, which conventional methods could not do. Immunotherapy techniques such as immune checkpoint inhibitors are used to alert checkpoints like CTLA-4 to activate killer cells (Barrios). These methods have been proven through numerous studies as much more effective than chemotherapy for mitigating the

impacts of CM (Leonardi 2018).

CM and the Immune System

CM is one of the deadliest types of cancer due to its ability to evade the immune system by taking advantage of the body's immune checkpoints like Programmed cell death protein 1(PD-1), Programmed cell death ligand 1 (PD-L1), and Cytotoxic T cell-associated Antigen 4 (CTLA-4). T cells use PD-1 to detect and bind to PD-L1, preventing the T cells from attacking the cell that is expressing PD-L1. Because of this, many types of cancer use PD-L1 to prevent T cells from attacking and killing the cancerous cells. CM has been found to have high amounts of Programmed cell death protein 2 (PD-L2), which also suppresses T cell function. Another method cancers including CM use to evade detection is CTLA-4, which outcompetes protein CD28 to bind to the protein B7, which are supposed to activate T cells in a process called costimulation. CTLA-4 blocks this and therefore prevents the T cells from activating and attacking the cancers. The main types of immunotherapy used to treat CM are Immune checkpoint inhibitors (ICIs) and Adoptive cell therapy (ACT). The main ICIs used to treat CM include ipilimumab, which targets CTLA-4 to enable costimulation, as well as using pembrolizumab and nivolumab to disrupt interactions between PD-1 and PD-L1, allowing the T cells to attack the cancerous cells. These therapies revolutionized the treatment of metastatic CM (Eddy 2020). The first method of ACT used to treat CM are Tumor-infiltrating lymphocytes (TILs) which expand the patient's T cells in a lab before reinfusing them with the patient. This method has a success rate over 50%; however, it needs T cells that are already activated, which causes TILs to be ineffective because many melanoma patients lack T cells that can fight against cancer (Zhao 2022). To overcome this barrier, a therapy that genetically modified T cells to have tumor-specific T-cell receptors (TCRs) was developed. TCRs recognize cancer based on Major histocompatibility complex I (MHC I); however, many cancers reduce the production of MHC I, resulting in an abysmal response rate to TCRs of only 13%. In an attempt to improve this response rate, Chimeric Antigen Receptor T cell (CAR-T) therapy was developed. CAR-T therapy works by engineering T cells that have a synthetic receptor that allows them to be able to recognize many different tumors and therefore enable T cells to recognize cancerous cells without MHC I. CAR-T therapy also fuses the first two signals of T cell activation, allowing them to be more easily and rapidly activated. Although CAR-T has been proven to be extremely effective in treating B cell malignancies, response rates in CM have been much lower (Eddy 2020). A preclinical trial aimed to test the impact of using DNA methyltransferase inhibitors (DNMTis) to trigger dsRNA in treating CM based on DNMTis results in Ovarian Cancer. These DNMTis treat cancer in two ways. The first is by preventing DNA methylation, a process by which cancer silences genes that are supposed to suppress the growth of tumors. The second is by increasing the expression of MHC I in healthy cells, allowing T cells to better differentiate between healthy and cancerous cells, boosting immune response (Chiapanelli 2015).

The Future of CM

There are currently many ongoing clinical trials to test new forms of immunotherapy in CM. The first one tests the combination of Talimogene Laherparepvec (T-VEC) and Pembrolizumab (NCT03842943). T-VEC is a modified oncolytic herpes virus that kills cancerous cells and releases granulocyte-macrophage colony stimulating factor (GM-CSF) which present tumor antigens to T cells, activating them. However, T-VEC on its own has been observed as ineffecient in improving the Overall Survival rate (OS) of patients, resulting in the need for further study in combination therapy (O'Donoghue 2016), which this study is attempting to accomplish. Pembrolizumab is a drug that allows the T cells to attack the cancerous cells by blocking PD-1 and preventing cancerous cells from using PD-L1 to deter T cells. Contrary to this study's plan, other studies show that there is no significant difference between monotherapy and combination therapy in melanoma (Almutairi 2020. The study is currently in Phase 2. Participants must have CM which has been mostly resected, and all mutation statuses are allowed. Patients cannot have a metastatic disease or mucosal or uveal melanoma or melanoma associated with immunodeficiency within the last 3 years. They also cannot have a history of autoimmune diseases or herpetic skin lesions. The study measures the Pathologic Complete Response to the combination of T-Vec and pembrolizumab in the lymph node over 6 months (NCT03842943). The second clinical trial attempts to find the relationship between the presence and quantity of cells expressing Interleukine 4 induced gene 1 (IL4I1) and CM to find the relevance of IL4I1 as a target of immunotherapy using both a retrospective and a longitudinal study. IL4I1 has been observed limiting CD8+ T cell response in melanoma, preventing the T cells from killing the cancerous cells; however, there is very limited research on the impact of ICIs on IL4I1. The study involves 3 groups of patients: a group made up of patients with primary thin melanoma, one with primary thick melanoma, and the last with stage III or IV unresectable melanoma, all of whom are required to have no other types of cancers as well as the patient and their family's approval of the study. Participants from group 3 will be excluded if they have a contraindication to xylocaine or do not have social security. To address prior limitations in the field, the study will use a retrospective study as well as a longitudinal study as well as using 3 different groups of patients suffering from CM. This will allow more accurate and realistic data on the impact of IL4I1 in CM (NCT04253080).

Conclusion

CM is a deadly type of skin cancer which claims tens of thousands of lives every year. Immunotherapy has become essential to the treatment of CM due to high rates of metastasis and unresectability. ICIs for PD-1, PD-L1, and CTLA-4 as well as different forms of ACT have made the effective treatment of unresectable CM possible, saving countless lives. Currently, researchers are working on ways to make immunotherapy for CM more successful by studying factors like combination therapies and other possible ICI targets. The future of immunotherapy in CM is bright as it is improving to the point where it can become the first choice when treating cancer.

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