Shining a Light on Melanoma: Illuminating Insights into Skin Cancer

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Cancer is a complex disease characterized by uncontrolled cell growth that can invade and spread to other parts of the body. Furthermore, the immune system is a network of cells, tissues, and organs that defends the body against infections and diseases. The immune system in the human body is to detect and destroy cancer cells. However, cancer can develop mechanisms to evade these defenses, therefore allowing cancer to grow and spread. To fight this, immunotherapy is a type of cancer treatment that harnesses the body's own immune system to attack cancer cells. Immunotherapy is attractive due to the fact that it has the potential to target cancer cells specifically while minimizing side effects compared to traditional treatments. These cells are part of the human body's natural immune response and are responsible for recognizing and destroying abnormal or cancerous cells. The immunotherapy aims to either enhance the activity of, or modify other immune cells to better attack the cancerous cells. This review explores how immunotherapy can overcome cancer immune evasion and examines its benefits in the context of Lentigo Maligna Melanoma.

Despite being a less common form of Melanoma, Lentigo Maligna Melanoma presents a unique challenge due to its slow-growing but invasive nature. The main cause of Lentigo Melanoma is genetic mutations, which can be seen to be very similar to other cancers, for example, the BRAF and NRAS mutations are the most commonly found mutations in Lentigo Melanoma (LLM). This disease affects those who are older at higher rates. However, while rare, cases have been observed in younger individuals as well (Cohen 2004). Many cases have the BRAF Mutation, which promotes the growth of and development of the Melanoma in the skin. Lentigo Maligna Melanoma affects males more commonly than females. Furthermore, those with fairer skin tones have Lentigo Maligna Melanoma more commonly, due to their skin having a lower level of melanin, which protects against ultraviolet rays from the sun. However, it should be noted that anyone of any skin tone can develop this disease. Humans in areas of higher ultraviolet light exposure are affected by this disease more commonly, for example, the disease can be noted in locations on and around the equator, where this can be seen the highest (DeWane 2019). Furthermore, localized lentigo melanoma has a high cure rate, therefore showing a high chance of survival without disease progression. Furthermore, 57 months after treatment, 95% of patients in the sample showed no further developments. People over 65 with Lentigo Melanoma have a 1-1.5% chance of developing LLM after treatment. Immunotherapy has had a significant impact in revolutionizing the care of these patients (Bub 2004). Other options are surgical excision which involves the removal of the entire cancerous region. Other treatment options include radiation therapy, which uses radiation, and is mostly for elderly and fragile patients. However, there are some side effects such as scarring and skin damage. Additionally, there is Cryotherapy which involves freezing the area with liquid nitrogen, but has a limited effectiveness for this variant of melanoma. (McLeod 2011).

Lentigo Melanoma can evade the immune system by developing a resistance to apoptosis. It may also reduce its expression of major histocompatibility complex (MHC) molecules, which are very important for presenting T cells with tumor antigens. LMM can also upregulate checkpoint regulators such as PD-L1, which interact with PD-1 to interact with T-cells to inhibit their activity. Furthermore, LMM tumors can attract regulatory T-cells (Tregs) and Myeloid-derived suppressor cells (MDSCs), which suppress the activity of the effector T-cells and create an immunosuppressive environment. The tumor cells also may secrete cytokines, like TGF-beta and IL-10, which advance the suppression of the immune response (Willemsen 2022). Immunotherapy for lentigo melanoma involves the use of checkpoint inhibitors, such as ipilimumab, nivolumab, pembrolizumab, and atezolizumab. These drugs work by blocking the checkpoint proteins on T-cells, which helps the immune system recognize and attack cancer cells. For example, the Imiquimod causes the activation of the T cells which fight off infected cells directly. Targeted therapy, such as BRAF and MEK inhibitors, can also be used in specific genetic mutations such as the BRAF V600E mutation. The immune cells typically targeted by immunotherapy for this disease are lymphocytes, specifically cytotoxic T-cells. The checkpoint inhibitors such as ipilimumab, nivolumab, pembrolizumab, and atezolizumab, have improved the treatment of melanoma due to their effectiveness in enhancing the human immune system's response against cancer cells (Vaienti 2023). Clinical trials have shown that these drugs can lead to durable responses and improved survival rates in patients with advanced melanoma. For example, the response rates have varied from approximately 30% to 50%. Some patients are able to achieve long-term remission, and those without an initial response may benefit upon further follow-up. The main target of the checkpoint inhibitors includes T cells. Although some may not have a response to immunotherapy for melanoma, further research and optimization may have a solution in the future. While checkpoint inhibitors, in the context of immunotherapy, have shown much efficiency in treating lentigo melanoma, there are some limitations. One major limitation is the fact that only 30% to 50% of patients respond, and some that do respond immediately may have disease progression later on. Furthermore, this can be related to other immune-related problems. These adverse effects can range from mild to severe and may require other treatment. These effects include damage or irritation to the skin such as redness, along with other less common effects like flu-like symptoms. Despite these limitations, immunotherapy has significantly improved the outcomes for many patients with melanoma, and ongoing research hopes to fight these limitations in the future. Though there are no FDA-approved immunotherapies for lentigo melanoma, there are some for melanoma in general, of which, may be effective in treating lentigo melanoma as well (Melanoma Treatment (PDQ®)–Health Professional Version 2019).

The study, (NCT01088737), is an article describing the potential of Imiquimod cream (5%) to eliminate residual LM following surgical excision. This study with a 5-year follow up-plan will enroll patients who underwent lentigo melanoma or lentigo Maligna melanoma surgery, in addition this trial is specifically labeled as phase 1 or the pilot phase. The subjects enrolled in this clinical trial are those that have had lentigo melanoma or lentigo Maligna melanoma. The

main criteria in this study was the requirement of treatment of Lentigo Maligna Melanoma. In this case, the imiquimod acts as an immunomodulator not a cell therapy, rather than introducing new immune cells, it stimulates the existing immune system to fight the cancerous cells or potential threats. Some limitations such as removing the tumor itself but having remains of the disease itself, is fought by the cream being used. By targeting the potential reservoir of lentigo melanoma cells, it has the potential to improve long-term outcomes for patients with Lentigo Melanoma and Lentigo Maligna melanoma (NCT01088737). There is an idea of a possible future direction to improve dosage levels and a schedule along with moving to phase 2 and 3. Furthermore, scientists hope to combine this therapy with others to improve efficiency. There is also a 5-year plan to advance this information and be able to expand as much as possible. However, the treatment after surgery is Imiquimod which is an immunomodulator, and is effective at reducing the affected area's size, by decreasing it. The phase of this study is the prospective, randomized, multicentre phase 3. Patients were randomly selected and assigned with a 1:1 ratio to either receive Imiquimod or a placebo for 4 weeks. Patients must have been through surgery to remove the Lentigo Maligna Melanoma tumor (NCT01720407). The Imiquimod cream being tested shows how it will be able to help the immune system. Furthermore, the true variability accuracy from patients can be measured. The future and advancement with this information will allow for further optimization and effectiveness of the Imiquimod cream.

This review focused on Lentigo Maligna Melanoma, a slow-growing skin cancer caused by sun exposure in areas like the face, ears, and arms. Immunotherapy shows promise for Lentigo Melanoma. Checkpoint inhibitors like ipilimumab and nivolumab help the immune system recognize and attack cancer cells. However, in the context of the use of Imiquimod, only 30% to 50% of patients responded, therefore highlighting the necessity of further optimization and research. Checkpoint inhibitors are the primary immunotherapy for Lentigo Melanoma. Challenges to overcome include overcoming non-responsiveness and immune-related side effects. Additionally, imiquimod cream is being explored as a permanent solution to either replace surgery or be used to eliminate any post-surgical residue of cancer cells. Immunotherapy has the potential to be a more significant treatment for Lentigo Melanoma. Ongoing research on optimizing existing therapies and exploring new options like Imiquimod cream could lead to improved response rates and even cures, which can be discovered through further testing. This article provides a detailed and systematic study about TRM Cells in human skin melanocytic lesions. The range is from healthy skin to metastatic melanoma. It is explained how TRM cells have been linked to improved survival of melanoma. Immunohistochemistry and multiplex immunofluorescence to analyze the expression of TRM-Associated markers in various skin lesions, with a large variety of samples. The article overall provides valuable insight into the role of TRM cells in melanoma and lays the foundation for future research in this area.

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