Use of Immunotherapy in Basal Cell Carcinoma Settings

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Overview of Cancer:

Cancer is a disease in which some of a body's cells grow and spread to other parts of the body uncontrollably. When cells get old or become damaged, they usually die. Cancer occurs when something in this process goes wrong. Cancer should be avoided by the body because of the immune system, which is a body's defense mechanism against disease and infection. It is made up of different tissues, cells, organs, and molecules that protect the body's cells. The immune system is designed to detect and get rid of abnormal cells, including cancer cells. Natural Killer (NK) cells and cytotoxic T lymphocytes (CTLs) are responsible for recognizing and killing cancer cells. These immune cells recognize the antigens on cancer cells, which they target and kill. Cancer cells can evade these immune mechanisms by downregulating the major histocompatibility complex molecule (MHC) so T-cells cannot recognize them as abnormal. If a cancer cell lacks MHC, NK cells will kill it. Cancer cells can also evade the immune system by blocking costimulation and therefore preventing T-cells from becoming activated and recognizing a cancer cell. Cancer cells can also upregulate immune checkpoints and turn T-cells off. Immunotherapy is a kind of treatment that helps the immune system fight diseases including cancer. Monoclonal antibodies, immune checkpoint inhibitors, and adoptive cell therapies are all types of immunotherapy treatments. Immunotherapy is a good option to overcome cancer immune invasion because it specifically targets the immune system to recognize and kill cancer cells which can be more precise than other treatments that affect healthy and cancerous cells during treatment. Immunotherapy can also oppose mechanisms that cancer cells suppress the immune response with, give the immune system a memory response to possible returning cancer which can help the body fight it off, and be combined with other treatments to make treatment more effective. Immunotherapy treatment is also personalized and typically has less severe side effects than other cancer treatments. In this review, we will cover the use of immunotherapy in Basal Cell Carcinoma (BCC) and the future direction this kind of treatment is headed in.

Overview of Basal Cell Carcinoma:

BCC is the most common type of human cancer, affecting 3.6 million Americans per year and making up 80% of skin cancers (Krakowski 2022). It is most commonly caused by ultraviolet (UV) exposure which damages DNA and induces tumor suppressor gene mutations (Krakowski 2022). When the mutation of tumor suppressor genes occurs, uncontrolled cell growth takes place which leads to tumor formation or growth (Krakowski 2022). In most cases of sporadic BCCs, mutations in different genes involved in the hedgehog (Hh) pathway have been found (Krakowski 2022). Hh genes are oncogenes. BCC is associated with mutations in PTCH1, PTCH2, SUFU and smoothed genes (Ungureanu, 2024). Although BCC is the most common cancer, it is the least likely to metastasize (Krakowski 2022). BCC's slow growth makes it more curable and less damaging the sooner it is treated. About 70% of BCC's are nodular which means this kind of cancer mainly appears in the form of a small lump (Krakowski 2022). BCC most commonly affects individuals with fair skin, aged above 50 years, with previous nonmelanoma skin cancer or family history of nonmelanoma, and people of male sex

(Seidl-Philipp 2021). Although these are the most commonly affected demographics for BCC, this cancer can also appear on women and skin of color. Diagnosing BCC on skin of color is more difficult due to its pigmentation and rarity, though (Krakowski 2022). Individuals with blonde and light blonde to red hair along with people who have light blue or green eyes also have an increased risk of BCC (Ungureanu 2024). People with freckles make up another demographic for a higher risk factor of BCC (Ungureanu 2024). In less than 1% of patients, BCC can progress and become metastatic or locally advanced (Ungureanu, 2024). The median survival rate for patients with metastatic BCC is 8-14 months, with a 5 year survival rate of 10% (Ungureanu, 2024). BCC can be treated with standard surgery or immunotherapy and prevented with sunscreen and minimized UV exposure (Krakowski 2022). Although UV exposure is the primary risk factor for BCC, other risks include using indoor tanning devices, radiotherapy, and alcohol consumption (Ungureanu 2024). Smoking is also a risk of more aggressive BCC variants because it is linked to increased mast cell numbers which is what more aggressive BCC cases are associated with (Ungureanu 2024).

Use of Immunotherapy in BCC Settings:

BCC evades the immune system in a few ways. One way the disease evades the immune system is by expressing proteins that avoid an immune response. For instance, Programmed Cell Death Ligand 1 (PD-L1) is a protein that binds to its receptor, Programmed Cell Death 1 (Pd-1), on T cells (Lipson and Evan 2017). The protein prevents the activation of T cells by sending an inhibitory signal (Lipson and Evan 2017). This evasion helps the cancer cells grow. Another way BCC evades the immune system is through the dysregulation of Cancer-Associated Fibroblasts (CAFs). CAFs are an activated form of tissue-resident fibroblasts induced by UV exposure and tumor signal (Chiang, Strafford, Buell, Ramesh, Amit, Nagarajan, Migden, and Yaniv 2023). CAFs secrete various chemokines, cytokines, and extracellular matrix proteins which downregulate a host's anti-tumor response (Chiang, Strafford, Buell, Ramesh, Amit, Nagarajan, Migden, and Yaniv 2023). M2 macrophages also dysregulate and promote tumor growth. Tumor-Associated Macrophages (TAMs) are a subtype of M2 macrophages that activate tumor-promoting genes in BCC (Chiang, Strafford, Buell, Ramesh, Amit, Nagarajan, Migden, and Yaniv 2023). M2 macrophages have a higher volume in the BCC microenvironment than other macrophages (Chiang, Strafford, Buell, Ramesh, Amit, Nagarajan, Migden, and Yaniv 2023). Metastatic BCC (mBCC) and locally advanced BCC (laBCC) cases consider immunotherapy as a treatment option. Current immunotherapy for Basal Cell Carcinoma includes PD-1/PD-L1 inhibition therapy (Li, Wang, and Lu 2024). Cemiplimab is the first immune checkpoint inhibitor (ICI) approved by the Food and Drug Administration for BCC (Li, Wang, and Lu 2024). Cemiplimab, which is an antibody directed against PD1, is an inhibition therapy treatment (Li, Wang, and Lu 2024). Cemiplimab treatment is a good option for patients who cannot tolerate Hedgehog inhibitors (HHI) (Wilson 2022). In a phase II study (NCT03132636) involving 84 patients with laBCC and 54 patients with mBCC who were unresponsive to HHI treatment, 31% and 22.2% of patients demonstrated responses to Cemiplimab treatment (Potestio, Scalvenzi, Lallas, Martora, Guerriero, Fornaro, Marano, and Villani 2024). Cemiplimab also has its limitations because not all patients will respond to this kind of treatment. Pembrolizumab, another monoclonal antibody, inhibits PD-1 (Li, Wang, and Lu 2024). Nivolumab is another kind of treatment, which is an antibody that combines with PD-1 and prohibits it and its ligand to have an interaction (Li, Wang, and Lu 2024). Atezolizumab, a PD-L1

inhibitor, is another kind of treatment (Li, Wang, and Lu 2024). An additional kind of treatment for BCC is Ipilimumab, which is a CTLA-4 inhibition therapy. Ipilimumab is an antibody against CTLA-4 which activates T lymphocytes and promotes proliferation by blocking the CTLA-4 inhibitory signaling pathway (Li, Wang, and Lu 2024). Ipilimumab can infiltrate into tumor tissues and cause death to cancer cells (Li, Wang, and Lu 2024). Relatlimab is the last kind of immunotherapy treatment. It is an LAG-3 inhibition therapy that binds to LAG-3 on T regs which blocks immunosuppressive signals and enhances the immune cell's anti-tumor effects (Li, Wang, and Lu 2024). An MDPI study tested mice and assessed tumor response to Ablative Fractional Laser (AFL) and anti-programmed cell death1 therapy (aPD-1). Olesen and others found that aPD-1 with AFL further promoted mouse survival, improved tumor clearance, and growth rates. aPD-1 combined with AFL also increased neutrophil counts, the proportion of MHCII-positive neutrophils, and CD4+ and CD8+ T cell infiltration (Olesen, Wiinberg, Lerche, Jæhger, Andresen, and Haedersdal 2021). Overall, Olesen and others found that AFL can serve as an adjuvant for aPD-1 treatments of BCCs and improve tumor immune infiltration.

Innovation and Future Directions:

Clinical trial NCT04679480 is an ongoing clinical trial that evaluates how an advanced BCC tumor responds to a combination of an anti-PD1 antibody and a pulsed HHI. 20 patients are being tested in this phase 2 trial with no blinding or randomization. All patients will receive a combination of an anti-PD1 antibody and a pulsed HHI therapy. To be included in this clinical trial, patients must have metastasized or locally advanced BCC not suitable for surgical or radio-therapeutic treatment, be over 18 years old, have an evaluable tumor, have an anticipated life expectancy of over 12 weeks, and have adequate organ function. Exclusion criteria for this trial consists of patient history of allergic reactions or acute hypersensitivity reactions to antibody treatments, Cemiplimab, excipients of Libtayo, doxycycline, tetracycline, Sonidegib, or excipients of Odomzo. Other exclusion criteria includes patient history of a solid organ transplant, history of drug or alcohol abuse. Patients receiving current treatment with another study drug, pregnant, breastfeeding, or receiving any anticancer treatment other than radiotherapy within 30 days of the initial administration of Cemiplimab are also excluded from this trial. Other exclusions include impaired cardiac function or heart disease, untreated brain metastasis that may be considered active, or evidence of new or enlarging brain metastases because these factors could impact the treatment and results. The clinical trial tests a Cemiplimab injection (Libtayo) and a HHI (Sonidegib). Cemiplimab will be a liquid dosage of 350 mg every 3 weeks starting at week 2 of the trial. The HHI (Sonidegib) will be a white 200 mg capsule orally administered once daily in a 2 week cycle every 4 weeks starting from week 0. The primary outcome measure of this study will be to identify the best response of the BCC tumor documented anytime during the 26 weeks the trial takes place. The secondary outcome measure will be the BCC tumor response at the very end of the trial (week 26). Another secondary outcome will be any histological changes detected in the BCC tumour. This trial addresses a popular immunotherapy treatment currently FDA approved for BCC, Cemiplimab. This trial has the possibility of making immunotherapy for BCC more effective because it aims to evaluate the response of a BCC tumor treated with a combination of the anti-PD1 antibody, Cemiplimab, and the pulsed hedgehog inhibitor, Sonidegib. Another clinical trial testing BCC is clinical trial NCT02834013. This phase 2 trial studies nivolumab and ipilimumab in treating patients with rare tumors including laBCC and mBCC tumors. To be included in this trial,

patients must have histologically and/or biochemically rare cancer and be above the age of 18 years. Patients with symptomatic interstitial lung disease, pneumonitis, any uncontrolled intercurrent illness, or an active autoimmune disease that has required systemic treatment in the past two years are excluded from this trial. Patients must also not have prior history of allergy or hypersensitivity to nivolumab or ipilimumab because allergy to treatment can cause dangerous side effects for patients or mess with the results of this trial. This trial is testing the ability of two different types of immunotherapy, ipilimumab and nivolumab, two monoclonal antibodies that may work to attack cancer cells' growth and spread. Nivolumab and ipilimumab are not standard treatments used for BCC, but they have potential. This study aims to progress these treatments so they can be used on BCC in the future. The clinical trial aims to have an outcome of an ORR. Secondary outcome measures for this study include OS and PFS.

Conclusion:

BCC is a common skin cancer typically caused by UV exposure. Immunotherapy is a treatment option for laBCC and mBCC cases and has shown promise when other treatments such as surgery don’t work. Immunotherapy does have its limitations due to the fact it is a personalized treatment and doesn’t work on every BCC patient, though. Currently, there are FDA approved immunotherapies for BCC such as PD-1/PD-L1 inhibition therapy, Cemiplimab, Pembrolizumab, Nivolumab, Atezolizumab, Ipilimumab, and Relatlimab. Immunotherapy has been impactful for patients intolerant to hedgehog pathway inhibitors or for patients who haven’t responded to other treatments. People are currently trying to find new treatments for laBCC and mBCC with clinical trials that test new immunotherapy drugs and combinations. In the future, immunotherapy could enhance treatment and management of BCC due to how many new treatments are being tested in clinical trials and showing promising results.

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