The Employment of Cancer Immunotherapy for Glioblastoma

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Introduction

Cancer is a group of diseases characterized by uncontrolled growth and spread of abnormal cells, which can result in death if not treated effectively. The immune system is our body's defense network, designed to fight off infections and diseases, including cancer. Ideally, the immune system should identify and destroy cancer cells. However, cancer can evade these mechanisms by disguising itself as normal cells or creating an environment that suppresses the immune response. Immunotherapy, a revolutionary approach to combating cancer, uses the body's own immune system as a weapon against the disease (Hilf 2018). Instead of directly attacking the cancer cells, as traditional treatments do, immunotherapy boosts or alters the immune system to more effectively identify and destroy cancer cells. This type of treatment includes a wide range of therapies, such as checkpoint inhibitors, which are drugs that block proteins on cancer cells or immune cells that would otherwise prevent the immune system from attacking the cancer cells (Hilf 2018). Immunotherapies have shown promise in treating a variety of cancers, but their effectiveness can vary greatly depending on the individual patient and the type of cancer. For example, in the case of glioblastoma, a severe form of brain cancer, patients have not seen significant improvements in their prognosis due to recent advancements in treatments that utilize checkpoint inhibitors (Hilf 2018). Despite these challenges, immunotherapy remains an attractive option for overcoming cancer immune evasion, particularly for glioblastoma (Brown 2022). One of the main reasons is that immunotherapy has the potential to specifically target cancer cells while sparing healthy cells. This could lead to fewer side effects than traditional treatments, which often damage healthy cells along with cancer cells. Furthermore, immunotherapy can potentially provide long-term protection against cancer, as the immune system can "remember" cancer cells and attack them if they return (Brown 2022). However, for immunotherapy to be successful, particularly treatments using checkpoint inhibitors, a high mutational load and responses to neoepitopes are generally thought to be essential. Unfortunately, glioblastomas tend to exhibit limited intratumoral infiltration of immune cells and typically contain only about 30-50 non-synonymous mutations, which can limit the effectiveness of these treatments (Hilf 2018). In this review, we will delve into the advancements in the field of cancer immunotherapy for glioblastoma, discussing the mechanisms of action, the challenges faced, and the potential future directions for research.

Main Body

Glioblastoma, a primary brain tumor, is one of the most prevalent and aggressive forms among adults. The exact cause of glioblastoma is unknown, but the disease has been linked to age, radiation exposure, and certain genetic syndromes. However, it is understood that glioblastoma begins when normal cells in the brain or spinal cord undergo changes in their DNA. These mutations allow cells to grow and divide at accelerated rates and continue living when healthy cells die. Over time, this abnormal cell division is what leads to masses of abnormal cells, or tumors, to form. This condition arises from mutations in genes that regulate receptor tyrosine kinase (RTK), rat sarcoma (RAS), phosphoinositide 3-kinase (PI3K), p53, and retinoblastoma protein (RB) signaling, such as in the *Epidermal Growth factor receptor (EGFR)*

gene. (Wirsching 2016) Some glioblastomas evolve from lower-grade gliomas, known as “secondary glioblastomas,” and can be broadly categorized into two types based on the presence or absence of specific point mutations in the genes encoding of isocitrate dehydrogenase (IDH) 1 or 2. IDH-mutant glioblastomas, though less common, are associated with a younger patient population and improved recovery. Glioblastoma predominantly affects older adults over the age of 45, with incidence rates peaking in the 75-84 age group. (Medikonda 2021) Men are more frequently diagnosed than women, and the disease is more common in developed countries, possibly due to better diagnostic facilities. Some studies also suggest a higher prevalence among white populations, although the reasons for this disparity remain unclear. (Shergalis 2018) Standard treatment for glioblastoma involves surgery, radiotherapy, and chemotherapy, with temozolomide being the drug of choice. The *O(6)-methylguanyl DNA methyltransferase* (MGMT) gene promoter can help choose treatments, especially in older patients. It suggests a good response to alkylating chemotherapy, a cancer treatment that damages cancer cell DNA to stop replication and cause cell death. (Yu MW 2021) However, this form of treatment has had a median survival rate of less than 15 months with current care, presenting the need for more effective therapies. Immunotherapy has emerged as a promising avenue for glioblastoma treatment, despite initial disappointments with checkpoint inhibitors and vaccine therapy in clinical trials. The tumor’s environment and multiple mechanisms of therapy resistance, including intra- and inter-tumoral heterogeneity, systemic immune system suppression, local immune dysfunction, and tumor plasticity, pose significant challenges to treatment. Additionally, interactions between the central nervous system and peripheral immune system add another layer of hurdles to immunotherapy for glioblastoma. Understanding the mechanisms of resistance may pave the way for the development of more effective immunotherapies against this cancer type.

Glioblastoma creates a protective environment that makes it difficult for the immune system to attack the tumor. One key way glioblastoma escapes immune detection is by producing substances that suppress immune cell activity and creating physical barriers like the blood-brain barrier (BBB), which limits the entry of immune cells into the brain. Several immune cell types are often dysregulated. Tumor-associated macrophages (TAMs), microglia (MG), and myeloid-derived suppressor cells (MDSCs) are commonly altered in the tumor microenvironment (TME). AMs, in particular, can be "re-educated" by the tumor to support its growth and suppress anti-tumor immune responses. Various immunotherapies are being explored to treat glioblastoma. One approach is targeting TAMs with colony-stimulating factor 1 receptor (CSF-1R) inhibitors, which are crucial for macrophage survival. Although CSF-1R inhibitors have shown promise in preclinical models by reprogramming TAMs to attack the tumor, their success in clinical trials has been limited. This is partly due to drug resistance mechanisms, such as alternative signaling pathways like PI3K. Another strategy involves vaccines that train the immune system to recognize and attack tumor-specific proteins, such as the mutated EGFRvIII protein in some glioblastomas. However, these vaccines have had mixed results, often due to the tumor's ability to lose these target proteins and evade immune attack. CAR T-cell therapy is another promising immunotherapy where a patient's own T cells are engineered to target specific tumor antigens. Despite its success in blood cancers, CAR T-cell therapy faces challenges in glioblastoma due to the tumor's ability to change its antigens and the immunosuppressive environment of the brain. Lastly, There are currently no FDA-approved immunotherapies specifically for glioblastoma. While many clinical trials are underway, the unique characteristics of glioblastoma, such as its heterogeneity and the protective barriers it

creates, make it difficult to develop effective immunotherapies. Additionally, the success seen in preclinical models often only translates to clinical benefit due to differences between animal models and human disease.

Immunotherapy, particularly the use of checkpoint inhibitors, has emerged as a promising strategy in combating glioblastoma, a severe form of brain cancer that has proven resistant to many conventional treatments. The development and application of immunotherapy for glioblastoma have been the focus of various clinical trials, with two notable ones being the study of ICT-107 (NCT ID: NCT01280552) and the combination of Ipilimumab and Nivolumab for MGMT-Unmethylated GBM (NCT ID: NCT04396860) (Medikonda 2021). The first trial, a Phase 2 study, enrolled 124 newly diagnosed GBM patients who had not yet received chemoradiation. This trial was testing ICT-107, an immunotherapy that utilizes dendritic cells (DC) pulsed with tumor-specific antigens to stimulate the patient's immune system to target and kill GBM cells (NCT ID: NCT01280552). ICT-107 aims to enhance the body's immune response against the tumor by using the patient's own white blood cells, which are cultured and exposed to synthetic peptides resembling GBM antigens. By leveraging dendritic cells to present tumor antigens to T cells, ICT-107 enhances the immune system's ability to recognize and attack tumor cells, addressing immune evasion by directly targeting tumor antigens (NCT ID: NCT01280552). The second trial, a Phase ⅔ study, enrolled 159 patients with newly diagnosed MGMT unmethylated glioblastoma. This trial compares standard radiotherapy with temozolomide against a combination of radiotherapy and immune checkpoint inhibitors, ipilimumab and nivolumab. These inhibitors are designed to help the immune system recognize and destroy cancer cells by inhibiting checkpoints that limit immune response (NCT ID: NCT04396860). This trial addresses the limitations of temozolomide's reduced efficacy in MGMT unmethylated GBM by exploring alternative treatments that might work better for this subset of patients (NCT ID: NCT04396860). These trials represent significant strides in the field of immunotherapy for glioblastoma. However, there is still much to be done. Future directions for these trials and the field as a whole involve exploring combination therapies, developing predictive biomarkers, ensuring long-term follow-up, integrating quality-of-life assessments, and utilizing adaptive trial designs to enhance personalized GBM treatment efficacy (Medikonda 2021). The innovation and future directions in the modern era for glioblastoma treatment are exciting and promising. As our understanding of the disease and the immune system's intricacies deepen, we can develop more targeted and effective treatments. By integrating patient-specific factors and using adaptive trial designs, we can ensure that each patient receives the most effective treatment for their specific case (Medikonda 2021).

Conclusion

In conclusion, this paper explored the complexities of glioblastoma, an aggressive and resistant form of brain cancer. Despite the promise shown by immunotherapy in treating various cancers, its effectiveness in glioblastoma has been limited due to the disease's unique characteristics. A variety of immunotherapies, including dendritic cell-based therapies, immune checkpoint inhibitors, and CAR T-cell therapy, are currently being investigated. While these have demonstrated potential in clinical trials, their overall impact remains limited due to the complexities of glioblastoma. Researchers are presently focusing on developing more effective immunotherapies, exploring combination therapies, and overcoming the challenges presented by the tumor's protective environment and its ability to evade the immune system. Looking

towards the future, immunotherapy holds significant potential in revolutionizing glioblastoma treatment. With continued research and innovation, we can look forward to more effective treatments that can significantly improve survival rates and quality of life for patients battling this challenging disease.

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