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New Horizons and Breakthroughs in the Therapeutic Treatments for Glioblastoma

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ABSTRACT

Glioblastoma represents a difficult challenge in both oncology and neurosurgery, characterized by its aggressive nature and poor prognosis. Despite its multimodal approach to standard treatment, combining surgery and chemoradiation therapy, the overall survival for patients remains disappointingly low. This review paper provides an overview of the clinical challenges associated with glioblastoma treatment, including tumor heterogeneity, low mutational burden, cancer stemness, and its immunosuppressive microenvironment. In addition, we explore promising future therapies such as the tumor treating fields (TTFields), carmustine wafer treatment, angiogenesis inhibition, CRISPR-Cas9 genome editing therapy, and immunotherapies such as dendritic cell vaccination (DCV) and immune checkpoint inhibitors (ICIs). Across the review, we highlight the potential, progress, and shortcomings of each therapeutic approach by addressing their respective success and challenges. By analyzing this information, we strive to provide a comprehensive review of the current progress of glioblastoma treatment and its future therapeutic potential.

Introduction

Glioblastoma, the most aggressive and lethal brain tumor, presents itself as a formidable challenge in both oncology and neurosurgery. With an annual incidence of approximately 3 cases per 100,000 individuals, glioblastoma is the majority of malignant brain tumors diagnosed (Tamimi & Juweid, 2017). Despite advances in neurosurgical techniques and therapies, the overall survival for patients diagnosed with glioblastoma remains dismally low, ranging from 12 to 18 months from the time of diagnosis (Nizamutdinov et al., 2018). In this review, we aim to provide an overview of glioblastoma treatments, ranging from traditional approaches to cutting-edge research and future directions, to enhance understanding and highlight strategies for patients battling this disease.

Clinical Challenges to Treating Glioblastoma

Despite efforts in research and clinical trials, the management of glioblastoma remains a clinical hurdle, characterized by complex tumor biology, treatment resistance, and constant recurrences. Glioblastoma sets up obstacles for treatment such as its high tumor heterogeneity, low mutational burden, immunosuppressive microenvironment, and its cancer cells' stem-like properties (Medikonda et al., 2020).

High Tumor Heterogeneity

Tumor heterogeneity is defined by the presence of different cell populations or clones carrying distinct biologic, genetic, or expression profiles within a tumor (Marusyk & Polyák, 2010), and it is a key characteristic of glioblastoma that not only confounds diagnosis but makes treatment targeting extremely difficult. Within its tumor

microenvironment, glioblastoma often exhibits many variations in its intratumoral and intertumoral characteristics, posing a substantial barrier to achieving an effective and standard treatment. The high tumor heterogeneity of glioblastoma complicates the development of effective therapies and underscores the need for personalized targeting approaches (Inda et al., 2014).

Low Tumor Mutational Burden

The cancer cells in glioblastoma have a low mutational burden (around 1~3 mutations per megabase), which limits the antigens in the cancer cells available for the immune system to recognize. Unlike tumors with a high mutational burden such as melanoma (around 14 mutations per megabase) (Hodis et al., 2012) or non-small cell lung cancer (around 19 mutations per megabase) (Ricciuti et al., 2022), which can cause robust immune responses, glioblastoma's low mutational burden reduces the effectiveness of the immune system in responding to the tumor (Nørøxe et al., n.d.). This phenomenon creates a significant challenge in stimulating the body's immune system to mount an effective antitumor response against glioblastoma.

Immune Checkpoints

Immune checkpoints such as Programmed Cell Death Ligand 1 (PD-L1) and Cytotoxic T Lymphocyte Antigen 4 (CTLA-4) are mechanisms that the tumors utilize to evade immune responses. Firstly, PD-L1 is a protein found on the surface of tumor cells, which interacts with its receptor Programmed Cell Death Protein 1 (PD-1), which is expressed on the surface of T-cells. When PD-L1 binds to PD-1, it sends inhibitory signals to the T-cells, which put brakes on their activation and function. Glioblastoma exploits this mechanism by upregulating PD-L1 expressions, allowing them to inhibit T-cell activation and suppress the immune system (Hao et al., 2020). In addition to PD-L1, CTLA-4 is another immune checkpoint protein that plays a critical role in regulating T-cell activation. CTLA-4 is highly expressed on the surface of regulatory T-cells (T_{REG}) within the tumor microenvironment. CTLA-4 competes with a co-stimulatory molecule on T-cells, CD28, for binding to the same ligand, CD80, on antigen-presenting cells (APCs). When the CD28 on the T-cells binds to the CD80 on an APC, a co-stimulatory signal is delivered, and T-cell activation and proliferation are enhanced. However, when CTLA-4 on T_{REG} binds to CD80, it transmits inhibitory signals to T-cells, dampening their activation (Liu et al., 2020). As a result, the CTLA-4 expression on T_{REG} contributes to glioblastoma's immunosuppressive environment by reducing T-cells' activity.

Immunosuppressive Tumor Microenvironment

The tumor microenvironment within glioblastoma is characterized by its intense immunosuppressive properties. Infiltrating immune cells, particularly microglia and macrophages, together named tumor-associated macrophages (TAMs), play a pivotal role in creating this immunosuppressive environment (DeCordova et al., 2020).

TAMs are initially recruited to the tumor site in response to a variety of chemo-attractants secreted by glioblastoma cells. Upon infiltration, TAMs can contribute to the growth and progression of glioblastoma by secreting growth factors, cytokines, and enzymes that promote tumor growth and angiogenesis. In addition, TAMs also possess immunosuppressive properties that actively diminish the immune responses of the body by secreting anti-inflammatory molecules such as interleukin-10 (IL-10) and transform growth-factor beta (TGF-β). IL-10 is a cytokine that plays a critical role in regulating immune responses and inflammation with abilities to suppress the function of immune cells such as T-cells and natural killer cells. Meanwhile, TGF-β enhances the immunosuppressive ability of GBM through an array of mechanisms such as preventing T-cell activation

and proliferation, inhibiting the activation of natural killer cells (DeCordova et al., 2020), and promoting the differentiation of T_{REG}, which, when bound to CTLA-4, can inhibit the activation of T-cells.

Glioma Stem-Like Cells (GSCs)

Glioma Stem-Like Cells (GSCs), as their name suggests, represent a subpopulation within glioblastoma characterized by their ability to self-renew and diverse differentiation potential. These cells possess stem cell-like properties, allowing them to fuel tumor growth and resist many therapeutic interventions. GSCs are also a main contributor to the high heterogeneity of glioblastoma and are thought to lead to consistent tumor recurrences (Ortensi et al., 2013).

One of the key abilities of GSCs is their ability to effectively evade immune responses. GSCs utilize various strategies to divert immune responses and create an immunosuppressive tumor microenvironment essential to the growth and progression of glioblastoma. One such mechanism is the down-regulation of major histocompatibility complex (MHC) class I molecules on the surface of GSCs. By reducing MHC class I expression, GSCs evade recognition by T-cells and natural killer cells, thereby escaping immune-mediated destruction (Audia et al., 2017).

Moreover, GSCs secrete immunosuppressive factors such as PD-L1 and transforming growth factor-beta (TGF-β), which exert inhibitory effects on T-cells (Audia et al., 2017). PD-L1 interacts with its receptor (PD-1) on activated T-cells, leading to the suppression of T-cell functions and activation. Similarly, TGF-β is an immunosuppressive cytokine that inhibits the activity of T cells and promotes the differentiation of T_{REG}, which is a subcategory of T-cells with highly expressed CTLA-4, an immune checkpoint protein that when bound to APCs can inhibit the activation of T-cells (Liu et al., 2020).

Standard Treatments for Glioblastoma

The current standard treatment for glioblastoma involves a multimodal approach, combining surgery, radiation therapy, and chemotherapy. Firstly, the surgical resection is a maximum safe resection that aims to remove as much of the tumor as possible while maintaining neurological function. Following surgery, adjuvant chemoradiation therapy will be administered to target residual tumor cells (Nam & De Groot, 2017).

Temozolomide (TMZ) is an oral alkylating agent that is used as the medication for chemotherapy. TMZ exerts its antitumor properties by methylating the guanine bases of the DNA of the cancer cells. Upon entering the cancer cell, TMZ releases a methyl group that can bind to many different locations within the DNA. However, TMZ is most valued for its ability to bind to the O6 position of guanine bases. Methylation at the O6 position of guanine is especially notable as it leads to mispairing with thymine. This mispairing can result in replication fork arrest and eventual apoptosis, thus inhibiting the proliferation of glioblastoma cells (Strobel et al., 2019).

Despite the multimodal approach, this standard suite of treatments continues to have a poor survival rate, offering a humbling 14-month median overall survival for patients who undergo all of the standard treatments. The poor prognosis of glioblastoma highlights the urgent need for novel therapeutic strategies that can effectively increase the survival rate of glioblastoma patients (Delgado-López & Corrales-García, 2016).

Ongoing and Promising Future Treatments for Glioblastoma

Despite the standard multimodal treatment for glioblastoma not changing for the past few decades, promising research and innovative treatments have arisen, demonstrating solid results in hopes of improving upon the current suite of treatments.

Tumor Treating Fields (TTFields)

Tumor treating fields (TTFields) is a locoregional treatment that inhibits mitosis and promotes apoptosis of proliferating cells through low-intensity, intermediate-frequency alternating electric fields applied to the skin of the scalp (Ram et al., 2021). Through the electrical current, directional force is exerted on the polar microtubules, and the assembly of spindle fiber is disrupted. This can result in mitotic arrest or delay of the proliferating cell due to the improper attachment of chromosomes to the spindle fibers. However, if these cells continue through mitosis, they will most likely produce abnormal daughter cells that will subsequently die in the next round of mitosis during interphase, undergo permanent mitotic arrest, or be subjected to further effects of TTFields if they continue to proliferate (Giladi et al., 2015).

TTFields have demonstrated solid results during the pivotal EF-14 trial which compared the effectiveness of TTFields with TMZ treatment versus TMZ alone (Ram et al., 2021). Patients who received TTFields with TMZ treatment reached a two-year survival rate of 43%, significantly higher than the 29% survival rate of those patients who only received TMZ treatment (Stupp et al., 2015). Notably, TTFields demonstrated significantly fewer adverse effects compared to chemotherapy. When combined with TMZ, TTFields showed no systemic toxicity, demonstrating its compatibility with chemotherapy. Compared to the sharp adverse effects of chemotherapy such as vomit and nausea, the most common side effect of TTFields is mild to moderate skin reactions right below the transducer array (Mehta et al., 2017).

In conclusion, TTFields demonstrates itself as a promising future treatment for glioblastoma, showing a significant increase in survival for patients and high compatibility with current standard treatments. With minimal adverse effects and notable success in clinical trials, TTFields has the potential to be considered for an additional part of the standard multimodal approach to glioblastoma treatment.

Carmustine Wafer Treatment

Carmustine wafer treatment, also known as the Gliadel® wafer treatment, is another innovative approach to glioblastoma management. Carmustine is an alkylating agent that is packed within biodegradable polymer wafers and placed within the surgical resection cavity following tumor removal surgery (Xiao et al., 2020). Upon implantation, the wafers gradually release carmustine into surrounding tissues. Carmustine exerts its cytotoxic effects by alkylating the guanine bases in DNA, thereby interfering with DNA replication and RNA transcription of proliferating tumor cells. Moreover, carmustine's high lipid solubility allows it to penetrate the blood-brain barrier, enhancing its ability to target any residual tumor cells (Li et al., 2023). Furthermore, the sustained release of carmustine from the wafers ensures prolonged exposure of residual tumor cells to the cytotoxic agent, reducing the likelihood of tumor recurrence around the surgical resection site, particularly for low-invasive types of glioblastoma (Ohnishi et al., 2022).

Throughout studies, carmustine wafers have been shown to increase the median overall survival of patients for around 2~4 months (Chaichana et al., 2011). However, the adverse effects of carmustine wafers also cannot be ignored. The most common adverse effect of carmustine wafer treatment is post-operative infections; additional potential adverse effects include seizures, healing defects, neurological worsening, bone marrow suppression, and pulmonary fibrosis (Li et al., 2023).

In short, carmustine wafer treatment offers a promising therapeutic approach in glioblastoma, enhancing patient survival rate through targeted cytotoxicity. However, the occurrence of adverse effects highlights the need for careful consideration and monitoring during its clinical application.

Angiogenesis Inhibition

One of the most central processes to glioblastoma progression is angiogenesis, where tumors stimulate the formation of new blood vessels to sustain their growth and metastasis. As a result, angiogenesis inhibition therapies are developed to counter this process. One of the most notable anti-angiogenic agents is bevacizumab (BEV), a monoclonal antibody that targets the vascular endothelial growth factor (VEGF), a signaling protein that plays a crucial role in promoting angiogenesis (Schulte et al., 2021). Within the tumor microenvironment, VEGF is highly expressed to stimulate angiogenesis. As a result, BEV is utilized as it specifically targets and binds to VEGF, thereby preventing it from interacting with its receptors on the surface of endothelial cells (Yu et al., 2015). By blocking this signaling pathway, BEV inhibits angiogenesis and deprives the tumor of blood and nutrient supply.

Unfortunately, BEV treatments have mostly received mixed results, with most studies unable to achieve any notable increase in median overall survival (Friedman et al., 2009). This is mostly due to the problem that, as BEV inhibits VEGF-dependent angiogenesis pathways, glioblastoma still has other VEGF-independent angiogenesis pathways that it can rely on (Gacche, 2015). As a result, only inhibiting one angiogenic pathway is not enough to completely deprive glioblastoma of blood.

In conclusion, while anti-angiogenic therapy has emerged as a prominent approach by targeting VEGF and impeding angiogenesis in glioblastoma, its efficacy remains questionable. Despite its ability to disrupt VEGF-dependent angiogenic pathways, glioblastoma cells can resort to alternative VEGF-independent mechanisms to sustain angiogenesis. This underscores the complexity of the tumor microenvironment and the need for multi-targeted approaches in combating glioblastoma progression for future research.

Dendritic Cell Vaccination (DCV)

Despite the immunosuppressive microenvironment being an inherent counter to any immunotherapy, dendritic cell vaccination (DCV) stands as a promising immunotherapeutic approach to treating glioblastoma. Dendritic cells are an integral part of the immune system, initiating and coordinating immune responses against pathogens as an APC. In DCV, dendritic cells are harvested from the patient's blood or bone marrow and undergo a process called antigen processing and presentation, where these dendritic cells are isolated and exposed to tumor-specific antigens that are obtained from the patient's tumor tissue sample. During this process, dendritic cells internalize the tumor antigens and display them on their cell surface. Once injected back into the patient's body, this presentation of tumor-specific antigens by dendritic cells will signal other immune cells such as T-cells to activate and initiate an immune response against the tumor (Schaller & Sampson, 2016).

Despite the promising process and intricate design of DCV, most studies on this therapy have not achieved significant success. Instead, they have yielded mixed results, failing to demonstrate a significant increase in median overall survival (Schaller & Sampson, 2016). These mixed outcomes are often attributed to the complexity of the immune system and the inherent immunosuppressive tumor microenvironment of glioblastoma. Despite efforts to activate T-cells using dendritic cells, numerous mechanisms exploited by glioblastoma effectively diminish this process. Notably, as mentioned in previous sections, T_{REG}, TAMs, and immune checkpoints are still inherent immunosuppressive properties of glioblastoma that are capable of dampening T-cell functions. As a result, DCV still struggles to mount a sufficiently robust immune response due to the effects of these immunosuppressive factors (Datsi & Sorg, 2021).

In summary, while challenges in treatment remain, continued research and innovation may still yield hope in effectively treating glioblastoma. With more understanding of the immune system or even combination with other immunotherapies, DCV may yet to realize its potential as an alternative treatment to glioblastoma.

Immune Checkpoint Inhibitors (ICIs)

In the face of the immunosuppressive tumor microenvironment of glioblastoma, which creates a significant challenge to all immunotherapies, approaches such as immune checkpoint inhibitors (ICIs) have emerged to reverse immunosuppression. ICIs are antibodies that function by blocking the interactions between checkpoint molecules (such as PD-L1 and CTLA-4) and their respective ligands (PD-1 and CD28) (Preusser et al., 2015). Typically, when PD-L1 and CTLA-4 bind to their respective ligands, they send out inhibitory signals to T-cells which dampens their activity (Liu et al., 2020). However, with ICIs that target these checkpoint molecules, they can prevent them from interacting with their ligands thereby reversing one of the immunosuppressive properties of glioblastoma.

Similar to that of DCV, ICI therapy has also not reached much success, failing to show an increase in the median overall survival of patients (Jackson et al., 2011). The disappointing results are mostly attributed to factors similar to that of many other immunotherapeutic approaches. Despite the blockade of immune checkpoints, many other immunosuppressive properties of glioblastoma, notably TAM infiltration and T_{REG}, remain difficult obstacles (Preusser et al., 2015). Additionally, the blood-brain barrier represents another challenge for the delivery of ICIs into the tumor site. However, efforts and discussions have been made about directly injecting ICIs into the cavity of surgical resection or utilizing wafers that are used in the carmustine wafer treatment to bypass the blood-brain barrier (Sanders & Debinski, 2020). However, combinational therapies that combine ICIs with other immunotherapies or standard chemoradiation therapies have also been receiving more attention (Ding et al., 2014). Further innovation in ICIs may reveal the true potential of this approach in glioblastoma treatment.

In short, while ICIs stand as a means to reverse immunosuppression, their efficacy in extending a patient's survival remains elusive. Many other challenges remain even with the blockade of ICIs. Nonetheless, ongoing efforts to address these challenges, including direct injection strategies and wafers, offer hope in enhancing the effectiveness of ICIs in treating glioblastoma.

CRISPR-Cas9 Gene Editing Therapy

The CRISPR-Cas9 system is a gene editing system that has been recognized in recent years for its potential to treat many different cancers. The system consists of two major components, the guide RNA and the Cas9 endonuclease enzyme. Firstly, the guide RNA will bind to the gene of interest, and the Cas9 enzyme will perform a double-strand DNA break, breaking the gene of interest away from the DNA strand (Al-Sammarraie & Ray, 2021). Afterwards, two mechanisms can happen, the non-homologous end joining (NHEJ) mechanism or the homology-directed repair (HDR) mechanism. The NHEJ mechanism involves repairing DNA by directly ligating the double-strand DNA break ends together, which may involve minor deletions or insertions (Jiang et al., 2013). On the other hand, when a donor DNA template is present, the HDR mechanism occurs and inserts the targeted DNA sequence from the donor DNA template directly into the DNA break in the host strand, allowing precise gene insertion (Dudáš & Chovanec, 2004).

CRISPR-Cas9 is often used to mediate gene knockdown or knockout for certain properties of glioblastoma that support its growth and progression. Notably, genes that are involved in apoptosis, inflammation, angiogenesis, self-renew abilities (cancer-stemness), invasion, and proliferation are glaring targets to be knocked down (Al-Sammarraie & Ray, 2021). Depending on the gene of interest, the CRISPR-Cas9 technology can properly pinpoint specific factors that need to be knocked down for specific treatments and patients.

Being a relatively new and novel therapeutic approach, the CRISPR-Cas9 system has shown its potential in cancer cell lines, being able to effectively knock down certain gene expressions that would otherwise

be a problem for treatment. In addition, the CRISPR-Cas9 system has demonstrated extreme flexibility, being able to manipulate genes of many properties, contrasting other immunotherapeutic approaches that can often only target one specific pathway. However, very few in vivo experiments on this system have been done for glioblastoma, and there may still be many other factors that need to be considered even with certain genes knocked down. Regardless, the CRISPR-Cas9 gene editing therapy is a promising therapeutic approach that may offer more hope for glioblastoma patients.

Conclusion

In conclusion, glioblastoma remains one of the most challenging cancers to treat, characterized by its aggressive nature, complex tumor biology, and resistance to conventional treatments. The clinical hurdles associated with glioblastoma included its tumor heterogeneity, low mutational burden, immunosuppressive microenvironment, and GSCs, these all present individual challenges for every therapeutic approach.

Due to the low survival rate of patients even when undergoing the full standard treatment, many novel therapeutic approaches emerge. In this review, we summarized and reviewed a total of six novel treatments for glioblastoma that hold promise to improving the survival rate of glioblastoma patients, these include tumor treating fields, carmustine wafer treatment, angiogenesis inhibition, dendritic cell vaccination, immune check-point inhibitors, and the CRISPR-Cas9 gene editing therapy.

While these approaches show promise, it is essential to acknowledge the challenges and limitations each approach faces, including the mixed clinical outcomes, adverse effects, and the complicated cancer biology of glioblastoma that cannot be understated. In pursuit of improving the prognosis of glioblastoma patients, future research and innovations will be integral. By addressing the clinical challenges and leveraging current therapies, the future will hopefully hold promising treatments for individuals battling glioblastoma.

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