Glioblastoma Multiforme: Challenges and Advancements in Treatment

Casey Meskovich

Abstract

Glioblastoma multiforme (GBM) is a tumor that is initiated in glial cells, usually astrocytes. GBM presents difficulties in treatment due to the delocalization of tumor cells, inherent resistance to most cancer drugs, and the limited capacity of the brain to repair itself. Although most cancers have demonstrated an increase in treatment efficacy associated with recent technologies, the recovery rate of GBM has remained stagnant over the years. Recent research, focusing on the immune response of the brain, has sparked hope for better treatments. This paper discusses why previous treatments have been ineffective and describes the recent advancements in treatment.

Introduction

One afternoon in September of 2018, Henry Leonard's office hummed with the clacking of computer keys and quiet chatter between coworkers–and, Henry's snoring. He had been asleep at his desk for approximately fifteen minutes before a concerned colleague shook him awake. Taking a sip of his coffee, Henry dismissed his lethargy as a symptom of aging; he had always been healthy and didn't see any other explanation. He squinted at his computer, unsure of what he'd been working on before falling asleep, and sighed. It was open to an extensively chaotic weekly calendar. Typically, Henry took pride in being well-organized, but had recently found himself struggling to keep track of projects.

A dull ache throbbed in his temples as Henry considered the work he had to finish that day. Preferring to avoid medication when possible, Henry ignored the pain. As the day progressed, his headache developed into nauseating pain. For the first time in fifteen years, Henry swallowed an aspirin tablet.

The day trudged on, and Henry was happy to go home. Later that night, he called a close friend to discuss his overtiredness, but was met with anger rather than sympathy. Henry was shocked to learn that he had spoken to his friend the day before, and had been aggressive and barely lucid. He had no recollection of this conversation, and apologized profusely.

Later that month, Henry was diagnosed with glioblastoma multiforme, an advanced form of brain cancer. In hindsight, these were his first symptoms–disorganization, headaches, memory loss, and inexplicable aggression. It was a bleak prognosis for Henry; very little is known about the causes of the disease, and it is highly incurable. Despite being the most common type of brain tumor, treatments for GBM have shown minimal advancements compared to treatments for other types of brain cancer. GBM carries an average five-year survival rate of 7.2%, significantly lower than the overall five-year survival rate for all types of brain cancer, which stands at 13% (Nuffield Trust, 2023).

What is GBM?

GBM is a type of glioma. Gliomas originate from genetic mutations in glial cells, which provide physical and chemical support for neurons (NORD, n.d.). According to the World Health Organization, gliomas are divided into grades I-IV, depending on the degree of malignancy.

Grade I gliomas are typically benign and slow-growing, often associated with mutations in the neurofibromin I (NF I) gene, responsible for growth regulation (Roswell Park Comprehensive Cancer Center, n.d.).

Grade II and grade III gliomas, characterized by rapid growth, most often arise from mutations in the TP53 gene. This gene is responsible for the production of a tumor suppressor protein. Grades II and III are rare in children, but commonly manifest in young adults.

Grade IV gliomas are GBM, and are the most common and malignant (Roswell Park Comprehensive Cancer Center, n.d.). GBM is commonly seen in patients over 50 years of age. However, there is growing evidence that GBM can also develop in children, adolescents, and young adults. Tumors found in younger individuals, though, are genetically unique from those found in older adults (MDPI, n.d.).

GBM, in particular, develops from astrocytes (Fig. 1).

Figure 1. An astrocyte (Ferri, 2023).

Astrocytes have a multitude of functions within the brain, ranging from clearing excess neurotransmitters, to stabilizing and regulating the blood-brain barrier (BBB) (NCBI, 2023). Astrocytes make up the majority of cells in the central nervous system; this is unsurprising, considering their versatility.

Astrocytes also have a wide variety of locations within the central nervous system; as a result, GBM can start anywhere in the brain. However, it most commonly forms in the frontal and temporal lobes, which play roles in speech, movement, behavior, and memory. Resulting symptoms, then, coincide with these functions; headaches, drowsiness, personality changes, and memory loss are among the most common (Moffitt Cancer Center, n.d.).

The intensity of these symptoms is influenced by genetic, epigenetic, and microenvironmental factors. Uniquely, family history is not a factor; the majority of patients have no family history of cancerous brain tumors. There is, however, a correlation between GBM patients and the diagnosis of close family members–individuals with immediate relatives afflicted with GBM are twice as likely to develop the disease. The disease is linked to age, with a median age of 64, and is slightly more common in men. The only controllable risk factor for GBM is exposure to ionizing radiation therapy, as this can contribute to genetic mutations (Moffitt Cancer Center, n.d.).

In most cases, the exact cause of GBM is unknown. However, there are a few similarities between characteristics of patients; many harbor mutations in the IDHI, EGFR, PTEN, TP53, PI3K, and TERT genes, which are coincidentally among the most commonly mutated genes in human beings (NCBI, 2023). Although functions of these genes are generally different, they all play a role in cellular pathway signaling. In rare cases, GBM can be linked to certain genetic syndromes, such as Turcot syndrome and neurofibrosis type 1 (NCBI, 2023).

Current Therapies and Their Success Rates

For GBM patients, options are extremely limited, as GBM presents distinct challenges. Localization of brain tumors, the presence of the BBB, and the limited capacity of the brain to repair itself are among these challenges. Arguably the most, however, is the inherent resistance to conventional treatments (American Association of Neurological Surgeons, n.d.).

GBM cells have stem cell properties. They're able to self-renew and differentiate into different cell types. This means that tumors are often made of a number of different types of cells, a phenomenon referred to as heterogeneity (MDPI, n.d.). Additionally, cells are able to take on different functions or roles within any one tumor, and change these roles as needed. Cells in a tumor are able to interact dynamically, forming a flexible tumor environment (MDPI, n.d.). As a result, GBM is able to adapt quickly and effectively to external conditions (like, the presence of a new drug in the system). The plasticity (ability of tumors to change and adapt) of GBM, combined with the recurring nature of the tumors, presents a difficulty in treatment.

GBM is most commonly treated with surgery, followed by chemotherapy. Radiation therapy is also used, often after a surgery to destroy inaccessible cancerous cells. Each of these treatments are uniquely unsuccessful. In surgery, for example, the delocalization of the tumor presents a problem–GBM diffusely invades the brain, unlike tumors in other parts of the body. As a result, it's difficult to remove the entire tumor with surgery (NCBI, 2020).

The presence of barriers presents a challenge for chemotherapy. Both the blood-brain barrier (BBB) (Fig. 2) and the blood-tumor barrier (BTB) are in effect when treating GBM.

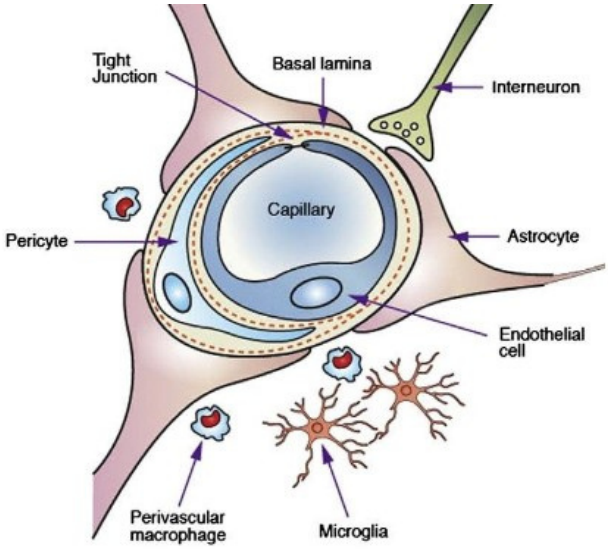

Figure 2. Diagram of the blood brain barrier (Parashar, 2012)

The blood vessels that vascularize in the CNS are highly selective, and function to regulate the movement of molecules between the blood and the brain, resulting in a membrane known as the blood-brain barrier (BBB) (NCBI, 2020). Tumors are known to compromise the BBB, resulting in vasculature called the BTB. The BTB is characterized by a non-uniform permeability, resulting from high heterogeneity (NCBI, 2019), and forms during the development of metastasis. As the tumor progresses, vasculature becomes increasingly heterogeneous. Normal vasculature is neatly arranged in a hierarchy of evenly spaced and well-differentiated arteries, capillaries, venules, and veins. Vessels supplying tumors (those that compromise the BTB) are increasingly chaotic, often following an irregular serpentine path (NCBI, 2010).

Selectively permeable barriers have been shown to reduce the effectiveness of cancer therapies for GBM. Current therapeutics have similar sizes to molecules that will not cross the BBB, such as recombinant proteins and peptides, antibodies, and viral vectors. This makes it difficult, if not impossible, to find therapeutics that cross into the brain.

Additionally, endothelial cells of vessels limit intercellular support of large hydrophilic drugs, a category many cancer drugs fall into (NCBI, 2023). These factors make many therapeutics ineffective in treating GBM.

GBM also exhibits interesting resistance patterns that make it difficult to treat. Resistance is most commonly acquired through the mechanism of DNA enzyme repair. Some cancer drugs (most notably temozolomide) create methyl adducts, which inhibit normal functions, on DNA. This modification is toxic to the cell's DNA and can trigger cell death. However, the repair enzyme O6-methylguanine-DNA methyltransferase (MGMT) is capable of reversing this methyl adduct, effectively repairing the damaged DNA before it leads to cell death (NCBI, 2020). This repair process prevents cell death and allows cancer cells to survive the chemotherapy's intended effects (NCBI, 2020).

Immunotherapies In Treating Cancer

While there are a few options available for GBM patients, immunotherapy is not one of them. Immunotherapy has been proven to be effective for various other cancers, including some that frequently metastasize to the brain. Melanoma, kidney cancer, and breast cancer are among these. However, as GBM does originate in the brain, immunotherapy has not been seen to be effective.

In tumors that don't originate in the brain (but may potentially metastasize to the brain), drugs called immune checkpoint inhibitors are used. Human immune systems have several checkpoints to regulate immune responses and prevent the immune system from attacking healthy cells. However, cancer cells can often take advantage of these checkpoints to avoid being attacked by the immune system. Immune checkpoint inhibitors are drugs that block these checkpoints, allowing it to recognize and attack cancer cells more effectively. These drugs have been found to elicit a significant increase in both active and exhausted T cells—signs that the T cells have been triggered to fight the cancer (Heady & Sun, 2023).

When the checkpoints are blocked, the immune system's killer T-cells become more active and capable of recognizing cancer cells as threats. T-cells are activated in lymph nodes. During this process, antigen presenting cells are recruited to the tumor, where they phagocytose dead or dying tumor cells (Heady & Sun, 2023). Receptors on the dead cells activate the antigen-presenting cells and these cells then migrate to the nearest lymph node and prime naïve T cells moving through there, allowing the immune system to continue to target the tumor (Branca, 2023).

In GBM, and other tumors originating in the brain, however, this T cell priming process isn't effective–leading to the lack of response to immunotherapy treatments. Researchers have found a significant difference in the way the two types of tumors (those that originate in the brain, and those that don't) respond to immunotherapy. In a study by UCLA, researchers aimed to specifically examine the effect of immune checkpoint inhibitors to explain the higher response of tumors originating outside of the brain to immunotherapy.

It was found that T cells in tumors that did not originate in the brain had characteristics that implied tumors were blocked from entering the brain (Heady & Sun, 2023). Immunotherapy led to a significant increase in T cell lymphocytes in brain metastases, but this increase was much smaller in patients with GBM (Heady & Sun, 2023). This data suggests that the priming circuit is not as effective in GBM, as T cells are best primed in draining lymph nodes outside of the brain–a process that is not possible for tumors originating inside of the brain. In the context of tumors, draining lymph nodes refer to lymph nodes that receive lymphatic drainage from the area surrounding a tumor. Tumors often stimulate the growth of new blood vessels and lymphatic vessels to support their growth and spread. As a result, tumor cells and antigens can enter the lymphatic system and be transported to nearby lymph nodes (Koukourakis & Giatromanolaki, 2022).

From these findings, researchers have suggested that dendritic cells are a potential therapeutic strategy. Dendritic cells are able to reach T cells in the brain, which lymph nodes cannot do. This process would include generating dendritic cells from patients in the lab, pulsing them with tumor-specific proteins, and then re-injecting them back into the same patient (Heady & Sun, 2023). By recreating the priming process in dendritic cells, the effects of lymph node activation can be re-created as well.

This poses exciting possibilities for the field of neuro-oncology. Currently, the UCLA researchers are attempting which immune cells are changing in the more responsive tumors to help better explain the higher response rate to the treatment. No study has comprehensively examined the differential effect of immune checkpoint blockade treatment on these two types of brain tumors (those that originate in the brain, and those that metastasize to it) before. In future studies, the researchers plan to analyze data from a larger, more uniform group of people who were diagnosed with melanoma that had spread to the brain (Branca, 2023).

Conclusion

Glioblastoma arises due to genetic mutations in these cells, causing uncontrolled growth. Unlike many brain tumors, treating glioblastoma presents specific hurdles. Challenges include the brain tumor's location, the BBB, and the brain's limited self-repair capacity. However, the most significant challenge is its inherent resistance to standard treatments.

While GBM has been generally difficult to treat, immunotherapy (which activates T-cells to target cancer cells) has proven to be particularly unhelpful. New studies show that this could potentially be due to a T-cell priming step that occurs outside of the brain, whereas GBM originates in the brain. Ongoing research into T-cell activation by dendritic cells offers hope for patients like Henry Leonard.

Moving forward, many scientists suggest a holistic approach that combines innovative therapies, personalized medicine, and current chemotherapies. This collective momentum in research not only aims to improve survival rates but also prioritizes enhancing the quality of life for individuals facing this challenging diagnosis.

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