Current Developments and Future Possibilities of Glioblastoma Treatment

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Abstract

Glioblastoma is one of the deadliest forms of cancer. It mainly occurs in the brain but can also be found in the spinal cord and is associated with aggressive proliferation and high treatment resistance. Researchers are looking for more effective treatments and ways to improve patient survival times as the prognosis for most patients is only about 14-15 months. The standard of care for glioblastoma currently involves surgery along with temozolomide chemotherapy and radiation therapy, but these treatments are often unable to combat the tumor successfully. Perhaps the most promising field of potential future treatments is immunotherapy, in which treatment is designed to stimulate the immune system to target the tumor. This article will specifically discuss two types of immunotherapies: vaccine immunotherapy, in which the patient's immune system is conditioned to fight the tumor through the introduction of tumor specific antigens, and CAR-T cell therapy, in which modified T cells are introduced into the patient intravenously.

Introduction: What is Glioblastoma?

Glioblastoma, also known as glioblastoma multiforme or GBM, is a particularly aggressive form of cancer that affects the central nervous system. It arises mainly from astrocytes, which are cells in the CNS that support the functioning of neurons by regulating neurotransmitter levels, stabilizing synapses, maintaining homeostasis in the extracellular space, and performing other important functions. GBM is the most common type of brain cancer in adults, and the risk of acquiring it increases with age. The incidence rates of diagnosis gradually increase from about 0.16 in children under 19 years of age to about 13.05 in the 65-74 year age range and 15.24 in the 74-84 year age range (Ostrom, 2015). The known risk factor for GBM is exposure to ionizing radiation, most commonly in the form of x-rays or other high-energy therapeutic radiation used to treat childhood tumors. Other risk factors include certain genetic disorders, such as neurofibromatosis, tuberous sclerosis, and other syndromes that seem to provide a predisposition for developing GBM (Nelson, 2012). Some potential risk factors include head trauma, certain medications, and exposure to various other agents, but the cause of GBM is still unknown (Nelson, 2012). GBM has a very poor prognosis - most patients are expected to live about 14-15 months after diagnosis - and is the most common type of glioma. The poor prognosis of GBM is due to the cancer's aggressiveness and the difficulty of treatment.

There are many characteristics of GBM that make it particularly dangerous and difficult to treat. It is known as a "quiet tumor," meaning it has low levels of tumor-infiltrating T cells. T cells are an important part of the immune system that help the body fight infection and, in cancer patients, tumors. The brain has many layers of tissue that surround and protect it, but that also keeps the level of T cells inside relatively low (Evans, 2019).Because it is difficult for T cells to get inside the brain, it is also difficult for them to fight GBM.

This, along with the fact that GBM tends to be highly heterogeneous, means GBM is one of the most immunosuppressive types of tumors. Another aspect of GBM that makes it difficult to treat is the fact that any drugs used to treat the tumor must cross the blood-brain barrier (BBB), which is exceptionally good at maintaining homeostasis and keeping foreign chemicals, including GBM treatments, out of the brain.

The Blood-Brain Barrier

One of the main reasons why treatment of GBM is so difficult is because of the BBB, which is a collection of blood vessels, endothelial cells, and other cells that surrounds and protects the brain. It maintains homeostasis in the brain by regulating which chemicals and ions can move in and out, which is essential for healthy brain functioning (Daneman, 2015). However, this tight regulation of chemicals also makes delivering drugs to the brain difficult. The cells of the BBB are very tightly intertwined, making it difficult for large chemicals to get across. Even when a drug is delivered to the brain, the BBB often removes the drug very quickly in its effort to maintain homeostasis, which prevents the drug from combating the tumor effectively (Bender, 2018).

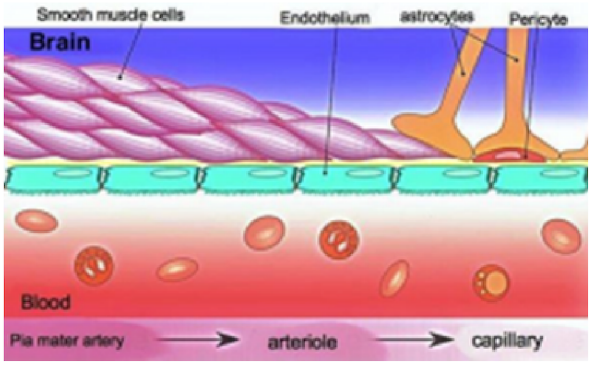

Fig. 1. A model of the blood brain barrier. Tightly joined endothelial cells line the blood vessels, creating a strong barrier to chemicals traveling into and out of the brain. Astrocytes, pericytes, and smooth muscle cells lend structural support to the endothelium. Evans, Taylor. 2020, April 17. How Pathogens Penetrate the Blood-Brain Barrier. American Society for Microbiology. https://asm.org/Articles/2020/April/How-Pathogens-Penetrate-the-Blood-Brain-Barrier.

An emerging technique to bypass the blood-brain barrier is called convection-enhanced delivery (CED). As opposed to typical systemic chemotherapy, CED involves placing catheters directly into the brain in or around the site of the tumor (Lambride, 2022). This process involves minimally invasive surgery and, in concept, is an easy way to bypass the BBB because it delivers the medication directly to the tumor. This technique also has an advantage over systemic chemotherapy because it reduces the toxicity in regions of healthy tissue and can limit its effects to the area directly surrounding the tumor (Lambride, 2022). However, since it is very difficult to examine the concentration of drugs in patients' brains, researchers usually must rely on computer models to predict the efficacy of this method (Lambride, 2022). Even with this limitation, CED could significantly improve the standard of care for glioblastoma by localizing chemotherapy and bypassing the blood-brain barrier.

Standard of Care

Currently, the standard initial treatment for GBM is surgery followed by radiotherapy and/or chemotherapy (Tan, 2020).If possible and relatively safe for the patient, surgery is linked to longer life expectancy when the extent of resection is very high. However, surgery is often difficult to perform without damaging healthy parts of the patient's brain, and it is not completely effective in removing all cancer cells (Tan, 2020). If surgery is not feasible, or after surgery is performed in patients in whom it is feasible, the next standard treatments include radiotherapy and chemotherapy. Radiation is directed toward the tumor site and surrounding areas, where it kills many remaining cancer cells (Tan, 2020). The FDA-approved chemotherapy drug for glioblastoma is temozolomide, which works by adding methyl groups to DNA's nitrogenous bases, disrupting the function of the cell and eventually leading to cell death (Fernandes, 2017). However, there are many problems with this treatment that prevent it from being an effective way to combat glioblastoma. Firstly, over 50% of patients are immune to temozolomide, and even more patients will acquire immunity over time as the treatment continues (Karachi, 2018). Secondly, temozolomide is known to negatively impact the immune system by reducing the number of lymphocytes in the body, which can cause unpleasant and dangerous side effects for the patient due to lower immune ability (Karachi, 2018). Because GBM is already a highly immunosuppressive form of cancer, this side effect of temozolomide is even more serious. Thirdly, temozolomide is usually unable to remove all cancer cells in the body and GBM often recurs within 6 months of treatment (Karachi, 2018). There is no standard treatment for GBM recurrence, but common treatment routes include additional surgery, treatment with different drugs, and repeated temozolomide treatment. Because of the difficulty and ineffectiveness of the standard treatments, researchers have been looking into new and better types of treatment.

Immunotherapy

Many potential immunotherapies are undergoing clinical trials, but there is currently no FDA-approved immunotherapy, and there is no concrete evidence yet that this type of treatment is effective. Additionally, the immunosuppressive nature of GBM makes immunotherapy an inherently difficult method of treatment. Nevertheless, researchers continue to test a wide variety of immunotherapies that could improve survival rates.

One type of potential immunotherapy involves vaccines designed to produce an immune response against tumor antigens. In vaccine immunotherapy, the patient is exposed to tumor specific or tumor-associated antigens along with immune-stimulating molecules in order to activate the body's immune response and make it easier for the immune system to target the tumor (McGranahan, 2019). Tumor-specific antigens, such as EGFRvIII, are antigens found only on GBM cells, while tumor-associated antigens, such as survivin, are not exclusively found on tumor cells but are rare enough in the rest of the body that they remain safe targets for treatment (McGranahan, 2019). These treatments are all still in clinical trials and, while some researchers find the results promising, they will require more testing and clinical trials before they can be used as official treatments. For example, in a clinical trial for a vaccine of the EGFRvIII antigen, a tumor-specific mutation of epidermal growth factor, the median overall survival was 20.1 months in the experimental group and 20.0 months in the control group, which is not a significant difference (Weller, 2017).In a clinical trial for a vaccine of the survivin antigen, an anti-apoptotic protein, the 12-month overall survival rate was 94.2%; however, this trial included a sample size of only 63 and did not include a control group (Ahluwalia, 2018). Additionally, many antigens are HLA-restricted, meaning the safety and efficacy of a vaccine depends on the antigens in the patient's immune system (McGranahan, 2019). Because of this, some vaccines will only be viable treatment options for a fraction of patients, and even if vaccines are proven to be effective treatments, they will not be available to everyone.

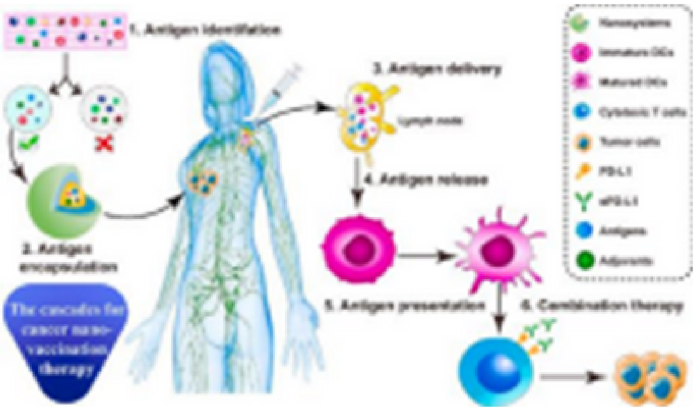

Fig. 2. A brief overview of how vaccine immunotherapy works. Tumor-specific antigens are identified and encapsulated to be delivered to the patient. Inside the patient, the antigens are released and presented to the immune system. Chen, F. et al. 2021. Nanomaterial-based vaccination immunotherapy of cancer. Biomaterials 270:10.1016/j.biomaterials.2021.120709

Another potential type of immunotherapy is CAR-T cell therapy. CAR-T cells are T cells that have been modified to recognize a tumor-associated antigen (Lambride, 2020). When administered into the patient's body, these cells target the tumor and activate other T cells to target the tumor. CAR-T cell therapy is already an established treatment for certain lymphomas and leukemias, so researchers are looking into applying it to GBM (Lambride, 2020). There are many antigens currently under investigation for CAR-T cell therapy, including IL13-Ra2, EGFRvIII, and HER-2 (Lambride, 2020). Similarly to vaccine immunotherapy, these treatments are still in the early stages of testing and clinical trials, and it is still unknown whether they will be viable treatment options. CAR-T cell therapy is potentially dangerous because it is known to produce toxicities, but so far, no clinical trials have shown significantly detrimental effects. As with other types of immunotherapies, more testing is necessary to determine whether CAR-T cell therapy is safe and effective as a GBM treatment.

Conclusion

The future of GBM treatment must involve new techniques and therapies such as convection-enhanced delivery and immunotherapy. The current standard of care is unable to put patients into remission consistently or to extend their lives significantly, and it often produces unpleasant and dangerous side effects. Though the fields of CED and immunotherapy are relatively new, they show more promise than the existing treatments, and researchers must continue to perform clinical trials to develop them into viable, effective, and safe treatments.

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