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Application of combination therapy for treating glioblastoma

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Abstract. Glioblastoma (GBM), an aggressive brain tumor with a high mortality rate, is also extremely easy to differentiate and metastasize, making it one of the most dangerous cancers in the world. The aim of this research was to establish a unique combination therapy that combines surgery and vaccination to treat GBM. This research uses predictive clinical trials and artificial intelligence analytics to summarize and examine the side effects and remedies of combination therapy, thus ensuring the physical and mental health of patients and aiming to create a low-cost treatment with a high success rate. Since angiogenesis is the most challenging side effect to treat, other remedies for this symptom were also summarized in this research. This means that this combination therapy may provide better success rates and a more patient-appropriate course of care compared to earlier approaches. It is hoped that in the coming time, this combination treatment plan will be adopted and implemented, and it is hoped that more efficient treatment methods will be proposed so that all GBM patients can be cured.

Keywords: Glioblastoma; Immunotherapy; Therapeutic vaccine; Adjuvants; Neoadjuvants.

1. Introduction

Cancer is a disease where cells multiply uncontrollably and spread throughout the body. It is a leading global cause of death, claiming about 10 million lives in 2020, representing one in six deaths [1]. Cancer can manifest as benign or malignant tumors, with glioblastoma (GBM) being one of the most lethal and challenging brain tumors. An abnormal cell growth in the brain is known as a brain tumor. Risk factors for brain tumors include exposure to radiation and a genetic predisposition to brain cancer. The incidence of brain tumors has been increasing across all age groups globally in recent years [2]. Common types of brain tumors in adults include meningiomas (low-grade), gliomas, and glioblastomas (high-grade). Low-grade tumors, when incompletely removed, have a 30% average 10-year survival rate and are less aggressive [3]. High-grade tumors, if untreated, have a median survival time of about three months and are more aggressive [4]. GBM is the most common and fatal brain tumor in adults, with over 300,000 new cases annually worldwide [5, 6]. Despite research efforts, only 15% of GBM patients survive five years, with an average life expectancy of 15 to 18 months post-diagnosis [6]. GBM not only has a high mortality rate but also severely impacts brain functions, emotions, behaviors, and cognitive processes, affecting patients' independent and identity. Treatment for GBM is expensive, creating financial burdens for patients and their families.

GBM has garnered attention due to its significantly higher mortality rate compared to other cancers, making it a crucial focus for research in the medical field. For GBM, treatment options include surgery, radiation, chemotherapy, and newer approaches like gene-editing techniques and vaccine therapies. However, the limitations of each treatment contribute to high mortality rates among patients, especially due to the challenging location of the tumor [7]. This has led to exploring combination therapy as a potential solution, drawing from past successes with surgery and vaccines [8]. Despite established clinical success with surgery, there is a lack of awareness regarding possible side effects and post-surgical reactions [9].

Simultaneously, experimental medications play a crucial role in ongoing research to combat GBM. These investigational drugs undergo rigorous review in clinical trials to assess their safety and efficacy. The U.S. Food and Drug Administration (FDA) plays a key role in authorizing investigational drugs for broader use based on positive outcomes [10]. GBM investigational

medications, including potential vaccines, are limited to clinical trials and extended access programs to ensure a safe study environment [11, 12]. For many patients, these investigational treatments may be their only viable option, underscoring the importance of continued research for GBM patients. Current research focuses on therapeutic vaccines for GBM. Therapeutic vaccines aim to boost the immune system's defenses in patients with the disease, but as of now, the FDA has not approved any therapeutic GBM vaccines for general use [13]. Access to these vaccines is currently limited to clinical trial participants.

This research presents a novel approach to treating GBM by combining surgical resection, gene editing, and a therapeutic vaccine. Using a vaccine alone is not sufficient due to the complexity of the disease. By integrating multiple technologies, this approach aims to address various aspects of tumor removal and cancer treatment comprehensively. Although limited by resources and experience, this work contributes significantly to GBM therapy research and development.

2. Strategies of combination therapy

The first clinical results of a personalized immunotherapy vaccine for recurrent, non-resectable, drug-resistant GBM are also reported [14, 15]. From the perspective of surgical treatment, several reviews of GBM treatment research based on data have discussed the trend of GBM treatment research [16]. A subsequent randomized clinical trial examined the impact of the oncology treatment field on health-related quality of life in patients with GBM, highlighting a common problem with the lack of quality-of-life data in many cancer clinical trials [17].

Combination therapy is divided into five parts. Based on the analysis of previous experiments and data, possible side effects are predicted through neoadjuvants chemotherapy, and the advantages and disadvantages of combination therapy are analyzed. The aim is to treat GBM completely and prevent secondary tumor formation using this method. The overall procedure of the experiment is as follows. After obtaining the tumor section, the first dose of vaccine is injected to stimulate the whole body's immune system to produce many of immune cells. The goal of this step is to make the tumor margin clearer. After that, blood tests and CT scans will be done to ensure that the immune system is activated and that the tumor is gradually becoming clearer and smaller. Surgery will then be performed to remove the cancer to relieve pressure on the nerves and brain. A PET CT will examine the patient for cancer cell metastasis and prevent the formation of a secondary tumor. Finally, a second dose of the vaccine reactivates the immune system to destroy all the hidden cancer cells and get the cure.

Before introducing the different parts separately, first extraction of Antigen from tumor cells will be need as part of the vaccine. It is worth mentioning that there are three kinds of antigens presented on the cell surface, namely: Tumor Protein p53 (TP53), Isocitrate Dehydrogenase I (IDH1), and Epidermal Growth Factor Receptor variant III (EGFRvIII). EGFRvIII will be choose as target antigen because it's more specific compared to others, as TP53 will appear in every tumor cell, and IDH1 will appear in low-grade gliomas while GBM belongs to high-grade tumors. After determining the targeted antigen, antigen will be purified from its tumor cells. It needs to obtain the tumor tissue samples as soon as possible after the surgery. Then, a blood sample is taken to separate antigens. A lysis buffer is used to disrupt cell membranes and release cytoplasmic proteins, which include tumor antigens. Then the homogenate is centrifuged at different speeds to separate whole cells, nuclei, and cell fragments from the supernatant. Leftover particles are filtered by passing through the membrane's suitable pore size. After that, separate the protein based on its size to isolate it from other proteins in the sample, and separate it according to its charge. For the last step, concentration of the purified antigen needs to be measured by using protein assays.

For the first step,viral-based vaccine will be chosen, which will best protect the nervous system in the brain. EGFRvIII has determined as the targeted antigen. Next, appropriate Neoadjuvants will be added-Anti-PD-1. which is a protein found on T-cells and inhibits T-cells to kill tumor cells. Because of the blood-brain barrier, chemical that leaks BBB needs to add in, so that more T-cells, after activating the immune system, flood in and attack the tumor. After the first round of screening, 5

different chemicals have been obtained, including Mannitol (an osmotic agent), Microbubbles (used in focus ultrasound), Histamine & Bradykinin (2 vasoactive substances), Radiation therapy, and Streptococcal Group A Toxins. Finally, Mannitol has been chosen as the chemical used. The main reason is that Mannitol will open the BBB by creating an osmotic gradient, while other methods will break BBB, which no one can make sure about when will BBB be cured again, and this makes it easier for inflammation in the brain by other pathogens. Intravenous injection will be the injection method been choosing. This provides a wider distribution, but more specialized medical personnel are needed and equipment as this type of injection needs more professional people. Diluents, which are normal saline (0.9% of NaCl), are used to maintain the concentration gradient in the vaccine and body and prevent bursts of the cell that occur during the efficiency of the vaccine. Gelatin will also be used, as it is a protein derived from collagen that can be used as a stabilizer in vaccines to protect vaccine antigens and stabilize vaccine formulations.

One or two weeks later, blood test and CT scan were performed. This step is simpler and the concept is fundamental, and the blood test is only to confirm whether the number of T-cells in the body has increased, to prove whether the first dose of vaccine is useful, can stimulate the immune system and trigger an immune response. The role of a CT scan is to confirm whether the tumor edge is clear, whether the tumor volume is smaller, and whether it is suitable for surgical removal.

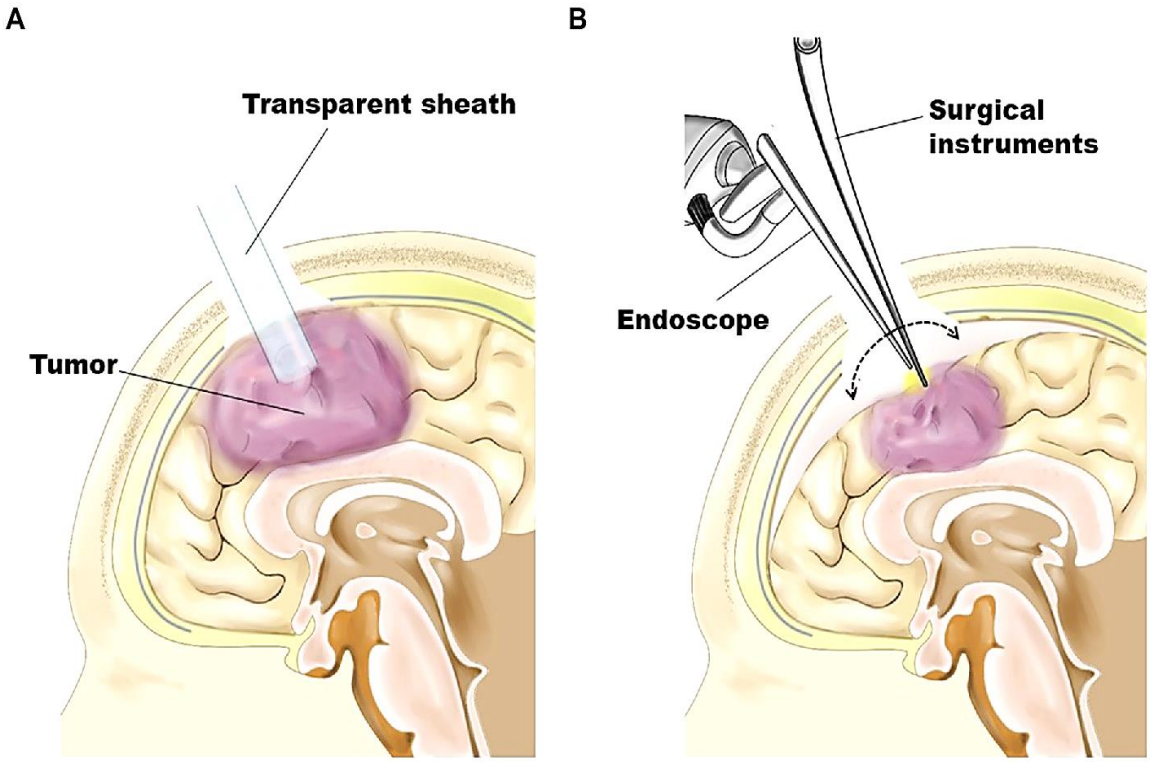

Figure 1. A diagram of the procedure. (A) is the first step, removing the tumor from the inside out. (B) Removal of the remnant by an outside-in approach [18].

A few days later, surgery will be involved to remove the tumor (Figure 1). The projection position of the tumor on the scalp body surface should be accurately located by manual measurement or using neural navigation according to the location of the tumor. Then, a horseshoe incision or curved incision should be marked on the scalp according to the location, and the scalp should be cut and opened to expose the skull. Holes should be drilled into the skull, a bone flap of appropriate size should be cut with a milling cutter, and the dura-exposed brain tissue should be cut. Since glioma is a tumor located in brain tissue, it is necessary to cut the brain tissue and then retract the brain tissue into the deep brain to expose and remove the tumor. Careful hemostasis should be performed after tumor removal to prevent the formation of intracranial hematoma after surgery. Then the dural is closed, the bone flap is reset, and the scalp is closed. Intraoperative ultrasonography and intraoperative magnetic resonance can be used to determine whether the tumor is completely resected.

PET CT will occur about one month after surgery. IVIS luciferase and radioactive tracer are added to the body, and gene plasmid of luciferase will be transfection into tumor cell's mRNA, which leads to the change in protein formation, after days, cell expansions and implantations, after luciferin is injected, all the cancer cells in the body will be highlighted on the PET CT scan report, to help doctors find out if cancer cells have metastasized in the body.

Finally, 1 week after the PET CT scan-the second dose of vaccine will be administered. IDH1 will be the antigen for the second dose because using the same antigen will make the second systemic immune response less effective, which is not acceptable. The adjuvants or booster used for the second vaccine will be R-613, as it's able to delay the development of the tumor masses. The same diluents and stabilizer will be used, as they're both efficient for both vaccines. Vaccines utilizing viruses modified to express tumor antigens are known as viral vector vaccines. Doses typically given intramuscularly or subcutaneously can vary from 1×10^8 to 1×10^{10} PFU. The big difference between the two vaccines is the immunomodulatory agents used in the second dose, which make sure the immune response goes normally, and will start with Checkpoint inhibitors, Toll-like receptor agonists and Cytokines Checkpoint inhibitors have been selected as Immunomodulatory agents. because it can provide higher survival rate than others, as one increase tumor size and the other has a higher probability for side effect to occur.

Due to equipment and time, only predicted trials can be provided and previous cases as experimental basis. Intravenous and subcutaneous injections will be used to inject the vaccine into the body. The mouse experiment will be performed first and then it will enter clinical trials. All trials will be double-blind so a placebo will be used. All the mice were subjected to the full set of tests. The purpose of these experiments is to determine whether survival can be improved and to find any side effects. 4 phases will occur in the predicted trials. Phase 1, in which 20-30 healthy people will be selected, and the therapy will be administered to them to check whether there are working and possible side effects the drug might have on the patients. For Phase 2, around 300 people will use in this phase to work more on the effectiveness of the therapy, and it continues working on safety even in this phase but is mostly restricted to checking out on the side effects that the drug might have on the patient. in Phase 3, several patients will be increasing, which the aim continues to be about safety and effectiveness of this therapy, but things changed in number of doses taken and time after each step, if the drug is approved by the concerned authorities or organization (FDA) after seeing the positive trial results, it proceeds to the final phase. For the last phase, after getting approval from the FDA the therapy is checked on diverse populations for safety and effectiveness.

3. Analysis of the effect of combination therapy

In general, the management of GBM involves a combination of treatment modalities, including surgery, radiation therapy, and chemotherapy. While surgery is important for diagnosis and providing symptom relief, the overall survival benefit of surgery alone is limited [19]. Careful consideration of the risks and benefits of each treatment approach is necessary when managing glioblastoma patients.

Based on prediction trials and past reviews, some possible side effects in vaccine injection and surgery treatment are inferred. Available evidence suggests that vaccines to treat GBM are generally well tolerated, with the most common side effects being mild such as fever and fatigue [20]. More serious side effects do not seem to be common. Ongoing studies are still evaluating the benefits of these vaccines in terms of increased survival. The side effects of steroids used in the treatment are common, and their frequency and severity increase with prolonged use. Surgery's role is to provide immediate mass effect relief, but adjuvant treatment such as radiation and chemotherapy is also typically applied [21, 22]. Long-term neurocognitive and other side effects can occur with radiotherapy, with or without chemotherapy, for glioma patients [22]. The simulation combined therapy was carried out with the help of AI. This therapy can solve or reduce most side effects, but there are always some inherent problems that are difficult to solve, and angiogenesis is one of them,

and it is also the deadliest. In this regard, literature from previous years have been summarized and the methods that have been studied.

Angiogenesis, the formation of new blood vessels, is a hallmark of glioblastoma and an important therapeutic target. Anti-angiogenic therapies targeting new blood vessel formation have been explored as a treatment for GBM [24, 25]. Some of the key anti-angiogenic agents that have been studied for the treatment of GBM include bevacizumab, sildenib, and afericept [26]. These drugs work by inhibiting signaling pathways that drive angiogenesis [27]. However, the clinical efficacy of anti-angiogenic therapies in glioblastoma is limited, involving treatment resistance and impact on the tumor microenvironment [25]. Combination therapy approaches that combine anti-angiogenic therapy with other treatment modalities, such as immunotherapy, are currently being explored to improve prognosis.

The treatment process is similar to the combined therapy. The key targets should be identified first. Vascular Endothelial Growth Factor (VEGF) and its receptor (VEGFRs) are used as targets. Clinical trials were conducted through 4 different methods to determine the best treatment plan. The first approach is to develop monoclonal antibodies, which will develop a specific binding antibody for the target, effectively prevent the receptor interaction of endothelial cells, and inhibit the formation of cardiovascular disease. However, the drug on the market is defective, and the side effect is too large, so many patients dare not use it. Small molecule inhibitors will also be an option, which block the signaling pathway of angiogenesis by inhibiting the activity of the enzyme produced by the receptor. In current drug development, there is no clear specificity to make the drug difficult to target a certain phenomenon, which will greatly reduce its effectiveness. Gene therapy, as a new program in recent years, is also within multiple consideration, and the steps are relatively simple, by encoding anti-angiogenic proteins and insert in tumor genes, the success rate seems to be high. The last approach, and the least widely used, is RNA-based therapies, which use siRNA to target and affect the expression of angiogenic receptors specifically. However, the disadvantages are also obvious, because RNA variability is extremely high, and the risk factor is therefore increased.

Combination therapy is also often used, including the combination of chemotherapy and radiotherapy, the combination of immunotherapy, is worthy of study, but generally speaking, the cost and use of higher and more difficult, while the side effects are not dare to think, so people are less used. However, the listing and solution of these problems indicate that the design of this combined therapy is progressing towards success.

4. Conclusion

The study of combination therapies to treat GBM is a critical moment in the field of brain tumors. This study conducted a rigorous combination therapy design, carefully evaluating solutions with different side effects. Through this predictive perspective, the study illuminates the profound ethical implications of combination therapy and what can happen later in treatment, while underscoring the urgent need for continued exploration and innovation in this area. Combination therapies designed to initially discover different treatments offer a beacon of hope for changing conditions that are difficult to treat with a ‘one shot’ vaccine. The analysis describes the potential for this type of therapy to significantly reduce the high cost and risk factors that are common barriers to patients and families wanting to pursue treatment. However, the road to widespread adoption of combination therapies is fraught with challenges, including vaccine hesitation due to concerns about safety and efficacy, economic barriers to access, and the potential for increased risk-taking behavior due to a false sense of security. This research highlights the paramount importance of ethical and equity considerations in the development of combination therapies. Ensuring equitable access to treatment, especially vaccines for marginalized and at-risk populations, is a cornerstone of ethical treatment distribution. Global collaboration and sustained funding were identified as essential elements to advance the development of new therapies. Investments in therapeutic technology and supply chain enhancement

have contributed to a shift toward rapid development and deployment capabilities, setting a precedent for future efforts in the therapeutic GBM research field.

In conclusion, this research not only contributes to the existing body of knowledge for GBM treatment development, but also catalyzes further discussion of the ethical, economic, and social implications of combination therapy research. While these findings indicate significant progress in the search for effective therapies, they also highlight the complex interplay of factors that influence the adoption and implementation of clinical trials. As the international community continues to grapple with GBM, the insights derived from the presentation of this novel combination therapy proposal can serve as a guiding light, highlighting the urgent need for innovation, collaboration, and ethical vigilance in the pursuit of a world free of malignant brain tumors.

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