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Glioblastoma Treatment Approaches: A Critical Review of Targeted, Immunological, and Physical Treatment Strategies

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Abstract. Glioblastoma is a group of highly heterogeneous abnormal tissue formations arising in the cerebral hemisphere. It stands as one of the cruelest and most aggressive brain tumors in adults, classified as a grade IV malignancy by the World Health Organization (WHO). Despite the wide range of advanced technologies & multimodality treatment employed to treat malignancies, the prognosis for patients with glioblastoma remains devastating; with a median survival ranging from 10 to 20 months with intensive therapy. Yet, in the face of these grim statistics, the past 15 years have witnessed remarkable progress in societies' understanding of glioblastoma's molecular landscape has increased tremendously. First, the article will discuss the overall landscape of glioblastoma, including its tumor microenvironment conditions, and it is severity compared to other categories of cancer prognosis. Then, investigate into the depths different treatments attempted in glioblastoma treatments, including targeting therapies, such as EGFR receptors, or CAR-T cell therapy. Then finally engaging into the multitudes of the new innovative physical modalities, such as the Gamma Knife radio surgery (GKRS), proton beam therapy (PBT), and Tumor Treating fields. While challenges such as tumor heterogeneity, antigen escape, and treatment resistance persist, the advancements made brought us a step closer to full remission.

Keywords: glioblastoma, cancer, immunotherapy

1. Introduction

Glioblastoma, constituting a highly heterogenous group of invasive malignant tumor groups, was the first tumor to go under comprehensive molecular characterization. It is lethal to a horrific degree, and the prognosis of glioblastoma was poor and persistent [1, 2]. Moreover, even after intense therapy, individuals affected by glioblastoma tend to have a survival period ranging from 10 -20 months depending on the severity of glioblastoma metastasis [3]. Thus, the mechanism and treatment of glioblastoma have been one of the most important topics for the past 15 years. Although glioblastoma and other brain cancer category morality rates have not yet budged, knowledge about glioblastoma has significantly broadened, bringing society a step closer to decreasing its fatality.

Although evolution within science from traditional radiation therapy, or curative surgery, physicians still have not found the most efficient way to surpass cases of glioblastoma, or cases of it are almost unavoidable for recurrourance [4, 5]. As today, controversies about the most effective

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treatment approach flourish, the current arsenal for recurrent disease relies on a combination of the following salvage strategies [6].

2. EGFR targeted therapy

EGFR targeted therapy comes to great significance due to the alteration found in half of glioblastoma cases due to the aberration in EGFR [7]. Statistics have shown that 20blastoma cases exhibit deletion of EGFR's exon 2-7 resulting in an oncogene that is consistent in its active phase promoting uncontrolled cell proliferation [2, 3]. This mutated EGFRvIIIin BS153 tendency to react with first generation EGFR tyrosine kinase inhibitors, such as erlotnib, and gefitinib. The unique BS153, capable of forming highly invasive tumors, tends to have growth patterns that are very unusual. Glioblastoma cell line has kept amplifying the EGFR gene and expression R vIII, which means to contract glioblastoma development, continuous cell proliferation must be cutback. Targeted therapy doses such as Erlotinib and Gefitinib can put a stop in glioblastoma proliferation by inhibiting the growth factor receptors of BS153, also limiting its migration, therefore preventing glioblastoma development. But sometimes, BS153 can develop resistance towards erlotinib but not gefitinib, due to the strong up-regulation of EGFRvIII and the ongoing activation of the PI3K pathways in BS153. But as the EGFR vIII in BS153 is knockdown, the sensitivity in erlotinib is regaining, and its functions in BS153 proliferation prevention becomes restored [2, 4]. Another example of a targeting vaccine is Rindopepimut, which is known as a vaccine to target the EGFR deletion mutation. Furthermore, Rindopepimut co comprises an EGFRvIII-targeting peptide conjugated to keyhole limpet haemocyanin [8]. Michael Waller and his team of possessional researchers in 2017 state the following conditions for his trials. In this randomized, double-blind, phase 3 trial, we recruited patients aged 18 years and older with glioblastoma from 165 hospitals in 22 countries. The result from the experiment demonstrates Rindopepimut in clinical applications for patients with newly diagnosed EGFRvIII expressing glioblastoma.

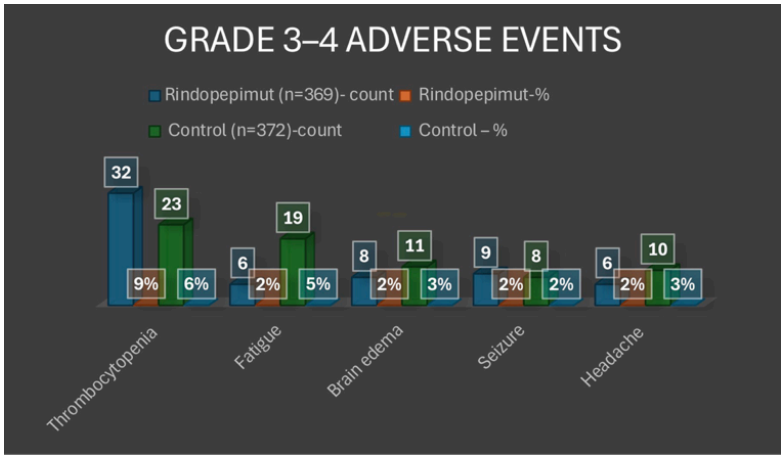


Figure 1. Grade 3-4 adverse events with Rindopepimut in glioblastoma treatment

Figure 1 presents the overall events occurring within the population of patients with minimal residual disease (MRD). The survival curves for the rindopepimut and control groups overlapped almost completely throughout the follow-up period, with median overall survival of 20.1 months (95% CI 18.5–22.1) versus 20.0 months (95% CI 18.1–21.9), respectively (hazard ratio 1.01 [95% CI 0.79–1.30]; p=0.93). The 12-month and 24-month landmark survival rates were also comparable between groups, and the curves demonstrated no significance evidence of late separation or delay

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upon the overall treatment effect upon the patient [8]. With the above data and conclusions about the use of this targeting antibody amongst newly diagnosed patients of glioblastoma cases, it has been highlighted how Rindopepimut conferred no survival advantages over the control in the MRD subgroup, confirming the inefficiency of this vaccine in this setting.

3. CAR-T cell therapy

Besides EGFR tyrosine kinase inhibitors that are used in targeting therapy, Chimeric Antigen Receptor T-cell therapy (CAR-T) is another glioblastoma treatment used when overcoming challenges due to antigen expression. CAR-T cells are chimeric antigen receptors that have been analyzed to have a T-cell receptor structure, and the activation of these receptors has set the path for T-cell based cancer therapies. The mechanisms of the CAR-T cells are efficient, as they can efficiently target the specific antigen and circumvent the activation process of endogenous T-cells for major histocompatibility complex (MHC)- Mediated antigen presentation. The therapeutic efficacy of these CAR-T cells are attributed to their seamless ability to recognize target surface antigens in a non-MHC-restricted manner, thereby appealing to the factor of their noteworthy productivity when it comes to circumventing the requirement for endogenous antigen processing and presentation human leukocyte antigens molecules. This mechanism explicitly displays the need for co-stimulatory signals from professional antigen-presenting cells and effectively neutralizes a major immune evasion strategy employed by malignancies—namely, the downregulation of MHC class I expression—while facilitating direct, rapid cytolysis of antigen-positive tumor cells.

3.1. CAR-T cell structural components & limitations

These CAR-T cells contain 4 domains: (1) an extracellular target antigen-binding domain, (2) a hinge region, (3) a transmembrane domain, and (4) one or more intracellular signaling domains (Sterner & Sterner, 2021). Each of these explicitly designed regions is for varying purposes. It is an antigen binding domain that is a single variable fragment composed of monoclonal antibody chains connected by a flexible linker; and is the part of the CAR that specifically targets antigens. The Hinge region provides flexibility to: (1) overcome steric hindrance, (2) targeted epitope accessibility form antigen-biding domains. The least understood region of the CAR cell is the transmembrane domain because they often change tailored on the requirements upon the extracellular spacer region or intracellular signaling domains. Furthermore, occurring to cite, research indicates that sufficient CAR-T cell signaling is achieved when the proximal intracellular domain is paired with its matching transmembrane domain, whereas expression and stability are improved using the commonly applied CD8a or CD28 transmembrane domains. Lastly, the intracellular signaling domains serve the purpose of translating antigen recognition into T-cell activation, proliferation, and cytolytic function —typically through immuno-receptor tyrosine-based activation motifs (ITAMs) derived from CD3ζ or co-stimulatory endo-domains like 4-1BB and CD28, which together determine the persistence and efficacy of the engineered T cells [9, 10].

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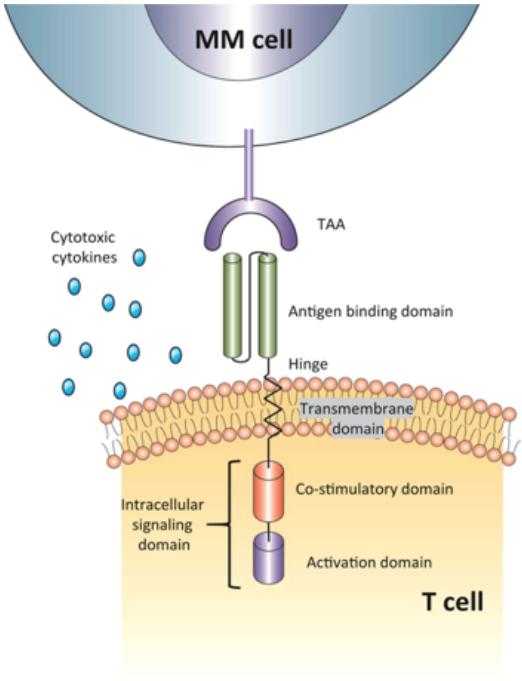


Figure 2. Various domains in the structure of a CAR-T cell [11]

3.2. CAR-T therapy flaws

As shown in fig 2, this version of cell therapy is currently in clinical trials for brain cancers, especially glioblastoma. But even after clinical efforts, CAR-T cell therapy cannot relieve the ongoing prognosis of the tumor microenvironment due to their insufficient number of specific antigens for Glioblastoma [9]. Another limitation of glioblastoma is the development of tumor resistance, leading to antigen escape [10]. Professor Christine E. Brown provided patients who have recurrent multifocal glioblastoma, with CAR– T cells targeting the tumor-associated antigen interleukin-13 receptor alpha 2 (IL13Rα2). Although the treatment was not associated with any toxic effects of grade 3 or higher, this caused a regression of all intracranial and spinal tumors, with a clinical response that continued 7.5 months after the initiation of therapy. But eventually, the disease recurred at four new locations after cycle 16 which was 228 days after the first treatment [12].

Many flaws in CAR-T cell treatment stated by Robert & Rosaline, state how first, solid tumor efficacy remains unestablished, where CAR-T cell therapy have once shown promising but limited efficiency against glioblastoma, with case studies demonstrating complete tumor regression for nearly 8 months (targeting IL-13Rα2) and median overall survival of 8–11 months (targeting HER2 and EGFRvIII). However, its efficacy remains restrained by major challenges including poor tumor infiltration, an immunosuppressive tumor microenvironment, antigen heterogeneity and loss (e.g., IL-13Rα2 down-regulation at relapse), and "on-target off-tumor" toxicity, contributing to an overall response rate of only 9% for solid tumors in meta-analyses [10, 13].

Another flaw is where the IL13Rα2 expression in the glioblastoma tumors is heterogeneous, which can limit effectiveness, due to its heterogenous nature. The limitation upon T-cell persistence and expansion is also noted. The CAR T-cell accumulation and expansion in the cerebrospinal fluid declined in later cycles of treatment, which may be driven by less antigen drive from decreased tumor burden or even immune rejection. One additional factor is tumor recurrence in new locations, due to the loss of antigens to battle the carcinoma. For example, in a CAR-T cell therapy case

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conducted, the researchers found the patient's glioblastoma eventually recurred at four new locations after, with preliminary results suggesting decreased expression of IL13Rα2 (antigen escape) as the cause. To further emphasize its potential limitations, poor trafficking to distant sites of CAR-T cells drove a failed intracavitary delivery to control tumors at distant intracranial and spinal sites, demonstrating how CAR-T cells are inefficient in trafficking to multifocal disease. Lastly, there are manufacturing limitations, where two separate CAR T-cell products had to be manufactured to obtain enough material for all infusions.

4. New innovative physical therapies:

Beyond conventional surgery & radiation therapy, recent technological advances have brought a new class of physical treatments aimed at minimizing glioblastoma , and damage to surrounding healthy tissue. Some major innovational physical therapy includes, Gamma Knife radio surgery (GKRS), proton beam therapy (PBT), and Tumor Treating fields.

4.1. Gamma knife radio surgery (GKRS)

Gamma knife radio-surgery (GKRS), developed in the late 1960s, delivers high levels of radiation doses to tumors. The array delivered is composed of about 200 sources of the decaying isotope, cobalt-60: capable of exerting photon beams, or gamma rays, targeting the ≤40mm tumor lesion [14, 15]. Karol Sadowski stated that Gamma knife radio surgeries have their advantages & disadvantages. An advantage of GKRS is less severed adverse side effects among patients, which means it is beneficial for recurring gliomas, but not recommended for newly diagnosed Glioblastoma. A disadvantage is that the tumor cannot be visualized well when they are above 40mm. Overall, GKRS has been proven to be effective in the management of recurring Glioblastoma [14].

4.2. Proton beam therapy (PBT)

Proton beam therapy (PBT) is another type of physical therapy that delivers high doses of radiation without affecting the surrounding healthy tissue, but unlike GKRS that treats recurrent small tumors, PBT known for being primary treatment, and treating low-grade gliomas [14, 16]. PBT is a major technological advancement in precision of radio therapy. In addition, PBT is clinically being employed in patients who have Glioblastoma because the potential of PBT in fight intracranial tumors has proved to be effective. To further emphasize the advantages of PBT for neurological tumors such as Glioblastoma, its side effects are acute for patients with low grade gliomas. This makes it a major technological advancement from past radiotherapies, including how there is a lowered risk in decline of cognitive functions compared to conventional photon radiotherapy after 2.5 years of post PBT treatment [16]. However, a key limitation as to why it is not generalized is due to its complex cyclotron or synchrotron targeting technology. Furthermore, it requires high levels of expense, planning, and detailed imaging, scaling down its efficiently. Overall, PBT is still well-praised physical therapy due to its precision, and reduction of major side effects, but further trials are needed for further improvement [14].

4.3. Tumor treating fields(TTF)

Tumor treating fields (TTF) is another type of physical therapy applied through electrodes applied to the patient's scalp. It is a non-invasive physical therapy modality that releases low intensity,

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intermediate frequencies that alternate in electric fields to disrupt cell division in highly proliferating tumor cells [14].

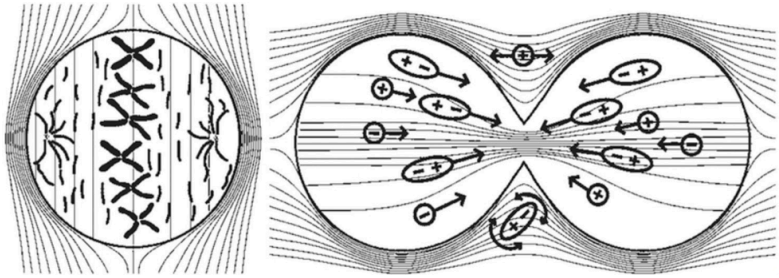


Figure 3. demonstration of mitosis disruption with alternating electric fields in TTF therapy [17]

In this process, the mechanisms of alternating electric fields disrupt the division of proliferating tumor cells. During the metaphase process of mitosis as shown on the left side of Fig.3, the electric fields remain uniform within the cell, and tumbling subunits align with the direction of field, and it inhibits their polymerization. This inferring force prevents the formation of normal microtubule spindles. Then, when the cells go under cytokinesis as shown on the right side of Fig.3, the electric fields become nonuniform with the dividing cell, which can drive dielectrophoresis, where the polar molecules go towards the high fields density area at the mitosis furrow. This process disrupts the mitotic stage of TTF therapy, leading to the disintegration of daughter cells [17].

The treatment conducted by TTFs through mitosis disruption is effective but has its flaws. One of its advantages is the ability to treat both newly diagnosed and recurrent glioblastoma. Moreover, it is approved by the Federal Food & Drug Administration (FDA), proving how it is efficient and safe for societal use. Further evidence is shown for its clinical efficiency, in the EF-14 phase III trial, TTFs maintained the temozolomide, and extended progression free survival by 2.7 months, and overall survival by 5 months compared to glioblastoma with temozolomide alone. But despite its efficiency & increase in survival periods, the costs are out of reach, and patience will need to continuously wear a device on their head, that causes the adverse events of TTF treatment, which are scalp-related dermatological side effects. But these side effects are less severe compared to other forms of physical treatment. Overall, TTF therapy is a significant landmark of neurological cancer treatment, and offers continuous, noninvasive opinion beyond traditional therapies [14].

5. Conclusion

Glioblastoma is still one of the most intrinsic research topics today, but despite research efforts, and significant landmarks, Glioblastoma remains one of the most lethal cancers today. Various researchers today are trying to approach glioblastoma from different cancer development points, such as the popular EGFR targeting antibody therapies, or CAR-T cell therapy, and the new innovative physical techniques. EGFR targeting therapies such as Erlotinib, Gefitinib, and Rindopepimut, have been clinically shown to have limitations due to glioblastoma resistance mechanisms, such as rindopepimut in phase III trials that have no survival advantages. But the CAR-T cell therapy demonstrated significant clinical potential, in how patients receiving IL-13Rα2-targeted CAR-T cells can achieve 8 months of tumor regression. But discouragingly, CAR-T cell therapy leads to poor tumor infiltration, antigen heterogeneity and loss, immunosuppressive tumor microenvironment, on-target off-tumor toxicity, and manufacturing limitations, contributing to an overall response rate of only 9% for solid tumors. Lastly, the physical therapies such as Gamma Knife radio surgery, proton beam therapy, and tumor-treating fields, offer treatment options where it

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is not invasive, and enhanced precision, such as the FDA approved TTF therapy. TTF therapy shows strong clinical evidence, with it is disadvantages being high costs, discomfort from scalp-related side effects. To sum up, while no single therapy has yet fully overcome the challenges of glioblastoma, every clinical trial brings us a bit closer, building upon the last, refining our understanding, and renewing hope for patients and their families. The progress made today in glioblastoma research stands as evidence for the dedication, collaboration, and funding of physicians, scientists, and institutions worldwide. Though the road ahead of us remains long and unknown, the hopes of achieving full recovery remind us to continue this innovation and persistence; to achieve a future where glioblastoma will no longer become a death sentence.

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