Novel Treatment Approaches to Glioblastoma multiforme: A systematic review.

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References and E-copy of Poster

Introduction and Objectives

Glioblastoma (GB), WHO Grade IV astrocytoma, is the most common primary brain tumor, accounting for 50.1% of malignant brain tumors[1]. The standard of care for the last two decades is based on the Stupp Regimen, which includes maximally safe tumor resection, chemotherapy with Temozolomide (TMZ), and radiotherapy (RT)[2]. Despite the improvements offered by this regimen, there remains a dismal prognosis with median overall survival (OS) of only 14.6 months[2]. Tumor Treating Fields (TTFields) recently became a recommended addition to the Stupp Regimen, increasing the median OS to 20.9 months[3]. Carmustine and Lomustine, available as IV infusions or implantable wafers, represent adjuncts approved for treatment of high-grade gliomas, but marginal improvement and limited data have prevented incorporation into the standard regimen[4]. Bevacizumab, the only additional treatment FDA-approved for GB in the last twenty years, has been most studied in recurrent disease[3]. There remains a critical need for novel therapeutics to treat GB, our study reports on three experimental treatments for GB and four recurrent GB (rGB) treatments.

The primary aims of this comprehensive review are to:

- Produce an up-to-date list of novel and experimental treatment approaches.
- Compare preliminary outcomes, including median OS and PFS.
- Highlight the most clinically significant novel treatments based on available preliminary data.

Methods

Keywords: *"Glioblastoma multiforme treatment", "Glioblastoma treatment", "Glioblastoma novel treatment", "glioblastoma novel therapeutics", "glioblastoma current treatment", "glioblastoma pathophysiology", "glioblastoma epidemiology", "glioblastoma clinical presentation", and "glioblastoma diagnostics"*

Databases: *Google Scholar, PubMed, ScienceDirect, BioMed Central*

First Filter: *Reading title and abstract, application of exclusion criteria.*

Second Filter: *Reading full-text, application of inclusion and exclusion criteria.*

Inclusion Criteria: *Up-to-date published articles available without payment, full-text articles, human studies*

Exclusion Criteria: *Non-peer-reviewed studies, focus on secondary GB, studies that included participants with tumors other than GB, animal studies, tumor model studies.*

Number of Studies: *70 articles were identified and reviewed for this study.*

Analysis: After a thorough review and consideration of full-text articles, relevant findings were extracted. Our team organized those findings to consider pathophysiology, epidemiology, clinical course, diagnostic methods, and current treatments of GB, in addition to our main objective, novel treatment methods. Efforts to consider all aspects of the tumor were made to enrich the understanding of available novel treatments in relation to improved patient outcomes and survival. The most significant end-points for each therapy category will be reported here.

Limitations

Numerous barriers exist and complicate the development and implementation of novel treatments. Overcoming the BBB to achieve adequate intra-tumoral therapeutic concentrations without inducing excessive collateral damage to nearby tissues remains a long-recognized and ongoing challenge. Poor clinical trial design with restricting inclusion criteria, small sample sizes, and inadequate control arms has hindered production of generalizable data and contributed to many late-phase trial failures. More thorough therapeutic characterization, including the ability to penetrate the BBB, in the preclinical stage and development of research models more representative of GB are needed to better elucidate potential treatment efficacy and make therapeutic development for GB more cost-effective. In respect to these limitations, only studies with both median OS and PFS reported were included, as one-year, two-year, and five-year survival rates were not reported in every study.

Results

Adaptive Radiotherapy

- Adaptive re-planning significantly lowers the dose of radiotherapy to healthy brain tissues by correcting for the differences in resection cavity absolute position among patients receiving RT[5-7].
- Patients with planning target volumes greater than 183 cm cubed had median OS of 28.98 months[8].

Synthesized Molecules

- Nivolumab, a monoclonal antibody directed at the programmed death-1 (Pd-1) checkpoint receptor, did not result in a greater increase of median OS compared to RT + TMZ[9].

Vaccines

- DCVax-L, a dendritic cell vaccine pulsed with tumor identifiers, administered in conjunction with the Stupp regimen, resulted in 23.1 months of median OS[10].
- PVSRIPO, recombinant non-pathogenic polio-rhinovirus chimera, which targets CD155, shows substantial tumor regression and prolonged overall survival in patients with rGBM[11,12].

Laser Interstitial Thermal Therapy (LITT)

- LITT directs low powered thermal energy to treat focalized tumor cells[13,14].
- NeuroBlate enhances the safety and effectiveness of LITT, demonstrating efficacy in rGB with a median OS of 10.4 months[13-15].

Enhanced Delivery Methods

- Low-intensity pulsed ultrasound (LIPU), high-frequency irreversible electroporation (H-FIRE), and convection-enhanced delivery (CED) show promise in delivering therapeutics across the blood-brain barrier (BBB), improving both median OS and PFS[16-20].
- LIPU-based disruption of the BBB increases the diffusion of chemotherapeutics such as Carboplatin resulting in the best median OS, 12.94 months[20].
- NanoTherm, intratumoral thermotherapy using magnetic iron-oxide nanoparticles combined with external beam RT, produced a median OS of 11.2 months when given alone[21].

STUDY	Treatment Algorithm	Median Survival Time (Mo)	Progression Free Survival Time (Mo)	One-year survival rate %	Two-year survival rate %	Five-year survival rate %
Thakkar et al., 2014	None	3	NA	NA	NA	NA
Stupp et al., 2005	Stupp regimen	14.6	6.9	61.1	26.5	NA
Végváry et al., 2020[8]	Adaptive RT	**(A)** 12.06	NA	~55 *	~30 *	NA
		(B) 28.98	NA	~90 *	~60 *	NA
Omuro et al., 2023[9]	Nivolumab + RT	13.4	6.0	58.3	10.3	NA
Liau et al., 2018[10]	Stupp + DCVax-L	23.1	NA	NA	NA	NA

Table 1: Comparison of novel primary treatment algorithms by median overall survival (OS) time, progression free survival (PFS) time, one-year survival rate, two-year survival rate, and five-year survival rate as data permits. **(A).** Change in planning target volume (PTV) less than or equal to 183 cm cubed. **(B).** Change in PTV greater than 183 cm cubed. **(*).** Data points have been extrapolated from provided graphs and figures, these are estimates. **(NA).** Data unavailable.

STUDY	Treatment Algorithm	Median Survival Time (Mo)	Progression Free Survival Time (Mo)	One-year survival rate %	Two-year survival rate %	Five-year survival rate %
Birzu et al., 2020	None	2 - 9	1.5 - 6	NA	NA	NA
Desjardins et al., 2018[11]	PVSRIPO + CED	12.5	NA	54	21	21
Sloan et al., 2013[15]	NeuroBlate	10.4	NA	NA	NA	NA
Idbaih et al., 2019[20]	LIPU + Carboplatin	12.94	4.11	NA	NA	NA
Maier-Hauff et al., 2010[21]	NanoTherm	11.2	NA	NA	NA	NA

Table 2: Comparison of novel treatment algorithms for rGB by median overall survival (OS) time, progression free survival (PFS) time, one-year survival rate, two-year survival rate, and five-year survival rate as data permits. **(NA).** Data unavailable.

Conclusions

In the novel treatment of GB we compared Adaptive RT, Nivolumab with RT, and Stupp with DCVax-L Vaccine to no treatment and the Stupp Regimen. The use of adaptive RT warranted the greatest increase in median OS, 14.38 months in comparison to the Stupp Regimen and a 25.98-month increase compared to no treatment. rGB benefits from more studies overall as the risk of no treatment, quantified by median OS of 2 to 9 months, is much higher than the experimental. In comparison of PVSRIPO, NeuroBlate, LIPU with Carboplatin, and NanoTherm, we demonstrated LIPU with Carboplatin to be the most efficacious treatment in regard to its median OS of 12.94 months. This benefit is an increase in the median OS between 3.94 and 10.94 months. Thus, we recommend the use of Adaptive RT instead of traditional focused beam RT in treatment of GB. In the case of rGB we recommend transiently modifying BBB diffusion with LIPU for the enhanced administration of chemotherapeutics, such as Carboplatin. Published data obtained from preliminary efficacy studies demonstrate the potential promise of novel technologies, as reported by increased median OS and/or PFS. Critically comprehensive treatment comparison is complicated by scarcity of published data, incomplete trials, and differences in measured study outcomes. It is also important to note that many of the novel therapeutics explored are examined for use as adjuncts to the current standard of care, highlighting that GB complexity and heterogeneity essentially necessitates a multimodal treatment approach. We look forward to a future in which the therapeutic arsenal is not only extensively broadened, but curative.