Glioblastoma Multiforme: A Comprehensive Review of Currently Approved Treatments

Greenberg, S., Brower, M., Rashid, M., Gademsey, A., Shahidi, R., Santiago, M., Kasper, B., Kasper., H., Perera, I., Marvin, E., Edward Via College of Osteopathic Medicine, Blacksburg, VA, 24060, USA

References and E-copy of Poster

Introduction and Objectives

Glioblastoma (GB) is the most common malignant brain tumor (50.1%), extremely aggressive, and denoted as Grade IV glioma by the WHO[1,2]. Although the exact cause is unknown, sporadic occurrence and high dose ionizing radiation are both linked to its incidence[2,3]. Unconfirmed risk factors that are related include certain rare genetic syndromes as well as occupational exposures[4], however there is currently no predictive measure for the development of Glioblastoma.

Presenting symptoms vary according to the affected brain region, with common symptoms including headache, dizziness, and visual disturbances[3,5]. The gold standard diagnostic is the contrast-enhanced brain MRI[5]. The median survival, even when treated, is 14 to 15 months[2,6].

The goal of this review is to:

- Provide a thorough efficacy analysis and overview of currently approved GB treatments.
- Compare treatments using median overall survival (OS), progression free survival (PFS), one-year survival rate, two-year survival rate, and five-year survival rate.
- Develop a recommendation for the best approved treatment regimen.

Methods

Keywords: *"Glioblastoma", "glioblastoma history", glioblastoma epidemiology", "glioblastoma pathophysiology", glioblastoma presentation", "glioblastoma clinical symptoms", "glioblastoma diagnostics", glioblastoma diagnostic imaging", and "glioblastoma current treatments".*

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 the full-text articles, all relevant findings were extracted. Our team organized those findings in a way to consider the pathophysiology, epidemiology, clinical course, diagnostic methods, and current treatments of GB. Efforts to consider all aspects of the tumor were made to enrich the understanding of available current treatments and to outline first, second-, and third-line treatments based on clinically significant findings.

Limitations

There are many factors that hinder the efficacy of current GB treatments. These factors include the impermeable blood-brain-barrier, the unpredictability of GB due to unknown epigenetic changes, tumor heterogeneity, and the presence of GB stem cells. Considering how each current therapy handles these limitations is an important step when determining the appropriate treatment. 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.

Discussion

The natural history of glioblastoma has a median OS time of 3 months[7]. Prior to the Stupp Regimen, maximal safe resection and targeted radiotherapy (RT) yielded a median survival time of 12.1 months; however, the current standard primary treatment, the Stupp regimen, has extended this time to 14.6 months[8].

Stupp Regimen

- Maximal safe resection is guided by functional imaging and fluorescence-based visualization to enhance the accuracy and extent of resection. RT is then administered stereotactically, or more accurately stereotaxically, to a standard dose of 60 Gy over 6 weeks[9,10].
- Therapeutic success of Temozolomide (TMZ) added therapy is rooted in the methylation status of the O6-methylguanine-DNA-methyltransferase (MGMT) promotor, which in its unmethylated state will repair the cytotoxic lesion created by TMZ at the O6-methylguanine[9,11-13]. The combined presence of methylated MGMT (methMGMT) and mutated isocitrate dehydrogenase (mIDH) possesses a better response to the Stupp Regimen; 35.8 months OS and 27.5 months PFS[14].

Tumor Treating Fields

- TTFields treatment utilizes an externally applied electric field emitted through a device connected to the patient's scalp via electrodes[11,15]. The low-intensity electric field waves alternate at 100-500 kHz interacting with certain proteins, disrupting formation of the mitotic spindle within rapidly dividing cells, leading to inhibition of mitosis, and ultimately apoptosis[15-17].
- Adding TTFields to the Stupp regimen increases the median OS to 20.9 and PFS to 6.7 months[9,15,18-20].

Carmustine Wafers

- Carmustine or Gliadel wafers are a local intracranially implantable chemotherapeutic delivery method FDA approved for GB treatment[11,21].
- The administration of an average of 8 Gliadel wafers given in conjunction with standard RT plus concurrent and adjuvant TMZ for GB improved median OS by 3 to 4 months compared to the Stupp regimen alone[21]. More recently, placement of greater than or equal to 12 Gliadel wafers improved median OS to 39.0 and PFS to 31.0 months[22].

Recurrent Glioblastoma Therapy

- Bevacizumab is FDA approved for second-line adjunctive use in the treatment of recurrent GB[9]. When Bevacizumab is administered with TMZ, there is a synergistic effect, increasing median OS by 6.6 months and PFS by 2.9 months compared to TMZ alone[23]. Patients have reported an increase in quality of life with Bevacizumab, but toxicity and adverse side effects still occur[23].

Study	Treatment Algorithm	Median OS (Mo)	PFS Time (Mo)	One-year survival rate %	Two-year survival rate %	Five-year survival rate %
Thakkar et al., 2014[7]	None	3	NA	NA	NA	NA
Stupp et al., 2005[8]	Maximal resection + RT	12.1	5.0	50.6	10.4	NA
Stupp et al., 2005[8]	Stupp regimen	14.6	6.9	61.1	26.5	NA
Yang et al., 2015[14]	Stupp + mIDH and methMGMT	35.8	27.5	69	NA	12
Stupp et al., 2017[15]	Stupp + TTFields	20.9	6.7	73	43	13
Ashby et al., 2016[21]	Stupp + Average of 8 Gliadel wafers	18.2	9.7	76.34	33.73	NA
Roux et al., 2023[22]	Stupp + ≥12 Gliadel wafers	39.0	31.0	NA	NA	NA

Table 1. Comparison of recommended 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. **(NA).** Data unavailable.

Conclusions

To summarize, GB continues to present a significant obstacle, as evidenced by its median survival time of 14 to 15 months, despite the implementation of the Stupp Regimen, the prevailing treatment approach. However, a review of all currently accepted treatments including Stupp with TTFields, Stupp with assessment of IDH and MGMT status, and Stupp with varying amounts of Gliadel wafers all demonstrate the benefit of adding to the Stupp regimen. We provide two recommendations. First, a therapy-focused approach, we recommend implementing the Stupp regimen with intracranial placement of 12 or more Gliadel wafers at the resection site as the chemotherapeutic portion, as this resulted in the greatest treatment-based benefit to the patient at 24.4 months and 36.0 months increased median OS compared to the standard Stupp regimen and no treatment, respectively. Secondly, a laboratory-focused approach, we recommend assessing for both mIDH and methMGMT status along with immediate initiation of the Stupp regimen as an indicator for potential treatment response. It is important to appreciate the various constraints that further limit these current treatments, including the blood-brain barrier, currently unidentified epigenetic alterations, tumor heterogeneity, and the existence of GB stem cells. It is essential to overcome these constraints to establish curative treatments in the very near future.