Regorafenib for glioblastoma

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Regorafenib, a multi-kinase inhibitor, has emerged as a potential therapeutic option for glioblastoma, particularly in cases where standard treatments such as surgery, radiation, and temozolomide chemotherapy have failed.

Mechanism of Action

Regorafenib targets multiple receptor tyrosine kinases involved in tumor proliferation, angiogenesis, and the tumor microenvironment, including:

VEGFR (Vascular Endothelial Growth Factor Receptors)

PDGFR (Platelet-Derived Growth Factor Receptors)

FGFR (Fibroblast Growth Factor Receptors)

KIT, RET, and BRAF These pathways are often dysregulated in glioblastoma, promoting tumor growth and resistance to standard therapies.

Clinical Evidence

REGOMA Trial (2019): A phase II clinical trial evaluated regorafenib in patients with recurrent glioblastoma:

Results: The study showed an improvement in overall survival (OS) compared to lomustine, a standard second-line therapy. Median OS for regorafenib was 7.4 months versus 5.6 months for lomustine. Implications: This result demonstrated the potential of regorafenib as a viable treatment option in recurrent settings. Ongoing Studies:

Further trials (e.g., phase III) are assessing its safety, efficacy, and potential biomarkers for predicting response. Studies are exploring combination therapies, such as regorafenib with immunotherapy, to overcome resistance mechanisms.

Potential Benefits

Angiogenesis Inhibition: Glioblastoma's hallmark feature is its high vascularity, making anti-angiogenic therapy a promising strategy. Tumor Microenvironment Modulation: Regorafenib can alter the tumor's supportive environment, potentially enhancing the efficacy of other treatments. Side Effects Regorafenib is associated with several adverse effects that require careful management, including:

Hypertension Hand-foot skin reactions Fatigue Diarrhea Hepatotoxicity Future Directions Biomarker Development: Identifying patients who would benefit most from regorafenib based on genetic and molecular tumor profiles. Combination Therapies: Combining regorafenib with checkpoint inhibitors, radiotherapy, or other targeted agents. Optimization of Dosing: Balancing efficacy with tolerability, particularly in patients with fragile health due to glioblastoma.

Meta-analysis of randomized controlled clinical trials

A meta-analysis, based on searches in PubMed and Web Of Science, evaluated 12 randomized controlled trials (RCTs) examining PKIs in patients with newly diagnosed or recurrent GBM. Pooled analysis of shared clinical outcomes - progression-free survival (PFS) and overall survival (OS) - revealed a lack of significant improvements with the use of PKIs. In newly diagnosed GBM, no significant differences were observed in median [-1.02 months, 95% confidence interval (CI), -2.37-0.32, p=0.14] and pooled [hazard ratio (HR)=1.13, 95% CI, 0.95-1.35, p=0.17) OS, or in median (0.34 months, 95% CI, -0.9-1.58, p=0.60) and pooled (HR=0.98, 95% CI, 0.76-1.27, p=0.89) PFS, when comparing PKI addition to standard chemo-radiotherapy versus chemo-radiotherapy alone. In recurrent GBM, three different analyses were conducted: PKI versus other treatments, PKI combined with other treatments versus those treatments alone, PKI versus PKI combined with other treatments. Also, across these analyses, no significant clinical benefits were found. For instance, when comparing PKI treatment with other treatments, median OS and PFS showed no significant difference (-0.78 months, 95% CI, -2.12-0.55, p=0.25; -0.23 months, 95% CI, -0.79-0.34, p=0.43, respectively), and similar non-significant results were observed in the pooled analyses (OS: HR=0.89, 95% CI, 0.59-1.32, p=0.55; PFS: HR=0.83, 95% CI, 0.63-1.11, p=0.21). Despite these overall negative findings, some data indicate improved clinical outcomes in a subset of GBM patients treated with certain PKIs (i.e., regorafenib) and encourage further research to identify PKIs with better blood-brain barrier penetration and lower risk for resistance development [1)]

This meta-analysis underscores the limited efficacy of current PKIs in GBM, despite rigorous

methodological approaches. While the findings are largely negative, the identification of potential benefits in specific patient subsets offers a pathway for refining PKI therapy. Future research should prioritize biomarker-driven trials, focus on agents with enhanced BBB penetration, and explore novel combination strategies. The ultimate challenge lies in overcoming the heterogeneity and treatment resistance characteristic of GBM, which remain formidable barriers to improving patient outcomes.

Systematic Reviews

Schettini et al. conducted a systematic review and Bayesian trial-level network metaanalysis (NMA) to identify the regimens associated with the best outcomes. The primary endpoint was overall survival (OS). Secondary endpoints were progression-free survival (PFS) and overall response rates (ORR). They estimated separate treatment rankings based on the surface under the cumulative ranking curve values. Only phase II/III prospective comparative trials were included.

Twenty-four studies (3733 patients and 27 different therapies) were ultimately included. Twenty-three different regimens were compared for OS, 21 for PFS, and 26 for ORR. When taking lomustine as a common comparator, only regorafenib was likely to be significantly superior in terms of OS (hazard ratio: 0.50, 95% credible interval: 0.33-0.75). Regorafenib was significantly superior to other 16 (69.6%) regimens, including NovoTTF-100A, bevacizumab monotherapy, and several bevacizumab-based combinations. Regarding PFS and ORR, no treatment was clearly superior to the others.

This NMA supports regorafenib as one of the best available options for relapsing/refractory glioblastoma. Lomustine, NovoTTF-100A, and bevacizumab emerge as other viable alternative regimens. However, evidence on regorafenib is controversial at best. Moreover, most studies were underpowered, with varying inclusion criteria and primary endpoints, and no longer adapted to the most recent glioblastoma classification. A paradigmatic change in clinical trials' design for relapsing/refractory glioblastoma and more effective treatments are urgently required [2)]

Schettini et al.'s systematic review and Bayesian NMA make an important contribution to understanding the relative efficacy of available therapies for relapsing/refractory GBM, particularly by highlighting regorafenib as a potentially effective option. However, the study is hindered by limitations inherent to the included trials and the analytical framework, including the heterogeneity of studies, underpowered designs, and outdated glioblastoma classifications.

The findings underscore the pressing need for a paradigm shift in GBM clinical trials. Future research should prioritize large, well-powered, multicenter trials incorporating molecularly stratified patient cohorts and harmonized endpoints. Additionally, the exploration of novel therapeutic strategies is critical to advancing the treatment landscape for this devastating disease. While regorafenib appears promising, its clinical utility must be validated in robust, contemporary trials to establish its place in the therapeutic arsenal for GBM.

Retrospective Studies

In a retrospective study, Kebir et al. investigated the efficacy and radiographic tumor growth patterns of regorafenib in recurrent high-grade astrocytoma.

They screened for patients with a high-grade astrocytoma in whom regorafenib was administered for at least 4 weeks. We assessed treatment efficacy in terms of progression-free survival (PFS), overall survival, and adverse events defined by Common Toxicity Criteria (CTC). In addition, radiographic tumor growth patterns were determined at baseline and recurrence.

A total of 6 patients met the eligibility criteria. The number of recurrences prior to regorafenib varied between 2 and 6. Patients were on regorafenib treatment for at least 4 weeks and maximally 14 weeks. Median PFS was 3.5 months and ranged from 2.0 to 4.0 months. Radiographic response was progressive disease in all patients with an objective response rate of 0%. CTC°3 adverse events were observed in all but one patient. The most common radiographic growth pattern was local with no change in growth pattern at recurrence. An infiltrative tumor growth was not induced in any patient.

This retrospective study indicates the very poor performance of regorafenib in recurrent high-grade astrocytoma with a fairly high number of CTC°3 adverse events. In addition, regorafenib does not seem to bear a potential for infiltrative tumor growth promotion [3)].

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