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protein kinase inhibitors as Targeted therapy for glioblastoma: A meta-analysis of randomized controlled clinical trials

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Abstract

Glioblastoma (GBM) is the most common and lethal primary brain tumor. The standard treatment for newly diagnosed GBM includes surgical resection, when feasible, followed by radiotherapy and temozolomide-based chemotherapy. Upon disease progression, the anti-vascular endothelial growth factor-A (VEGF-A) monoclonal antibody bevacizumab, can be considered. Given the limited efficacy of pharmacological treatments, particularly for the recurrent disease, several molecularly targeted interventions have been explored, such as small-molecule protein kinase inhibitors (PKIs), inhibiting tyrosine kinase growth factor receptors and downstream signaling pathways involved in GBM angiogenesis and infiltrative behavior. This 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.

Keywords: Abemaciclib (PubChem CID: 46220502); Afatinib (PubChem CID: 10184653); Axitinib (PubChem CID: 6450551); Bevacizumab (PubChem SID: 178103377); CC-115 (PubChem CID:

58298318); Cediranib (PubChem CID: 9933475); Cilengitide (PubChem CID: 176873); Dasatinib (PubChem CID: 3062316); Everolimus (PubChem CID: 6442177); Galunisertib (PubChem CID: 10090485); Gefitinib (PubChem CID: 123631); Lomustine (PubChem CID: 3950); Neratinib (PubChem CID: 9915743); Nimotuzumab (PubChem SID: 249565669); Regorafenib (PubChem CID: 11167602); Rindopepimut (PubChem CID: 139593451); Temozolomide (PubChem CID: 5394); Temsirolimus (PubChem CID: 6918289); Vandetanib (PubChem CID: 3081361); Veliparib (PubChem CID: 11960529; angiogenesis; glioblastoma; kinase inhibitors; receptor tyrosine kinases; targeted therapy; temozolomide.