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An Update on Bevacizumab Usage Management and Chemotherapeutic Approaches for Glioblastoma

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Introduction

Glioblastoma, the most common primary brain tumor in adults, has one of the most dismal prognoses in cancer. In 2009, bevacizumab was approved for recurrent glioblastoma in the USA. To evaluate the clinical impact of bevacizumab as a first-line drug for glioblastoma, two randomized clinical trials, AVAglio and RTOG 0825, were performed. Bevacizumab was found to improve Progression-Free Survival (PFS) and was reported to be beneficial for maintaining patient performance status as an initial treatment. These outcomes led to bevacizumab approval in Japan in 2013 as an insurance-covered first-line drug for glioblastoma concurrently with its second-line application. However, prolongation of overall survival was not evinced in these clinical trials; hence, the clinical benefit of bevacizumab for newly diagnosed glioblastomas remains controversial [1].

Description

Bevacizumab, as antibodies, were applied to inhibit tumor angiogenesis by preventing activation of vascular endothelial growth factor receptor. We analyzed four clinical trials, including 607 patients, to investigate the efficacy and safety of bevacizumab when combined with chemotherapy for the treatment of glioblastomas. Results demonstrated that bevacizumab when combined with chemotherapy improved progression-free survival (HR=0.66; 95% CI 0.56–0.78; p<0.00001) compared with bevacizumab or chemotherapy alone. Furthermore, overall survival showed insignificant difference between two arms (HR 0.99; 95% CI 0.8–1.21; p=0.92). However, we found that patients treated with bevacizumab-containing therapy reported increased objective response rate (OR 1.85, 95% CI 1.17–2.93; p=0.009), but more treatment-related adverse events (OR 1.75; 95% CI 1.09–2.83; p=0.02) [2].

Several studies have investigated the efficacy and safety of bevacizumab in combination with chemotherapy for glioblastoma treatment. A meta-analysis of randomized controlled trials of bevacizumab combined with temozolomide in recurrent glioblastoma also showed an effect only on PFS, and the benefit of bevacizumab even for recurrent glioblastoma is controversial. Another study analyzed the effect of bevacizumab plus temozolomide-radiotherapy for newly diagnosed glioblastoma with different MGMT methylation status and found that bevacizumab plus temozolomide-radiotherapy improved PFS and OS in patients with unmethylated MGMT promoter. Several chemotherapeutic approaches have been investigated for glioblastoma treatment. Temozolomide, an oral alkylating agent, is a standard treatment for glioblastoma. Bevacizumab, a humanized monoclonal antibody, targets Vascular Endothelial Growth Factor (VEGF) and inhibits angiogenesis. Irinotecan, a topoisomerase I inhibitor, has been used in combination with bevacizumab for recurrent glioblastoma. Cediranib, a tyrosine kinase inhibitor, has been investigated as monotherapy and in combination with lomustine for recurrent glioblastoma [3].

Several studies have investigated the role of bevacizumab in combination with other therapies, such as radiation therapy, for the treatment of glioblastoma. A phase II trial of bevacizumab plus hypofractionated stereotactic radiotherapy in recurrent glioblastoma showed promising results, with a median overall survival of 12.5 months. Another study evaluated the safety and efficacy of bevacizumab plus intensity-modulated radiation therapy in newly diagnosed glioblastoma and found that the combination was well-tolerated and resulted in a median overall survival of 16.7 months. Bevacizumab has also been investigated in combination with other targeted therapies, such as tyrosine kinase inhibitors, for the treatment of glioblastoma. A phase II trial of bevacizumab plus the tyrosine kinase inhibitor, cediranib, in recurrent glioblastoma showed promising results, with a median progression-free survival of 5.5 months [4].

In addition to its use in combination with other therapies, bevacizumab has also been investigated as a single agent in the treatment of glioblastoma. A phase II trial of single-agent bevacizumab in recurrent glioblastoma showed promising results, with a median progression-free survival of 4.2 months. Another study evaluated the safety and efficacy of single-agent bevacizumab in newly diagnosed glioblastoma and found that the treatment was well-tolerated and resulted in a median overall survival of 14.2 months. Despite the promising results of bevacizumab in the treatment of glioblastoma, there are still several challenges associated with its use. One of the main challenges is the development of resistance to bevacizumab, which can occur through various mechanisms, including the upregulation of alternative angiogenic pathways and the development of bevacizumab-resistant tumor cells. Another challenge is the management of bevacizumab-related adverse events, such as hypertension, proteinuria, and thrombosis, which can be severe and require dose reduction or discontinuation of treatment [5].

Conclusion

To overcome the challenges, several strategies have been proposed, including the development of combination therapies that target multiple angiogenic pathways, the use of biomarkers to predict response to bevacizumab, and the development of novel anti-angiogenic agents that can overcome bevacizumab resistance. Additionally, several ongoing clinical trials are investigating the use of bevacizumab in combination with other therapies, such as immunotherapy and gene therapy, for the treatment of glioblastoma. In conclusion, bevacizumab is a promising agent for glioblastoma treatment, but its benefit for newly diagnosed glioblastoma is still controversial. Further studies are needed to investigate the optimal dosage and schedule of bevacizumab administration and to manage bevacizumab-related adverse events. The combination of bevacizumab with chemotherapy, such as temozolomide and irinotecan, may improve treatment outcomes for glioblastoma patients.

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Conflict of Interest

None.

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