Bevacizumab for glioblastoma recurrence

Recurrent Glioblastoma: Bevacizumab is often used as a treatment option for recurrent glioblastoma, which means that the cancer has returned or progressed after initial treatment with surgery, radiation therapy, and chemotherapy. Bevacizumab may be considered in cases where other treatment options have been exhausted.

Maintenance Therapy: In some cases, bevacizumab may be used as maintenance therapy following initial treatment, especially in situations where the tumor has responded well to the standard therapies. Maintenance therapy aims to prolong the time before the cancer recurs.

Palliative Care: Bevacizumab can be used in palliative care for glioblastoma patients to help manage symptoms and improve quality of life. It may help reduce tumor-related symptoms such as edema (swelling), which can lead to better overall well-being for patients.

Clinical Trials: Bevacizumab may also be used in clinical trials for glioblastoma. Clinical trials investigate the safety and efficacy of new treatments or combinations of treatments, and bevacizumab may be part of these experimental therapies.

It's important to note that the use of bevacizumab in glioblastoma is a subject of ongoing research and debate in the medical community. While some studies have suggested potential benefits in terms of slowing disease progression and improving quality of life, others have shown mixed results. The decision to use bevacizumab in glioblastoma treatment is typically made on an individual basis, taking into account the patient's specific circumstances, the stage of the disease, and other factors.

Patients with glioblastoma should discuss their treatment options, including the potential use of bevacizumab, with their healthcare team to make informed decisions about their care.

Bevacizumab(Avastin®)– a monoclonal antibody against VEGF. FDA approved in May 2009 for progressive glioblastoma following prior treatment based on two trials: the BRAIN study, AVF3708g [1] and NCI 06-C-0064E [2].

Given as 10 mg/kg every 2 weeks until disease progression. The reported 6-month PFS rate was 36.0%. The median response durations were 3.9 months and 4.2 months from the two trials. The median OS was 9.3 months [3].

Side effects: gastrointestinal perforations, wound healing complications, hemorrhage, fistula formation, arterial thromboembolic events, hypertension.

Faltings et al. first reported the effect of rechallenging a patient with super-selective intra-arterial cerebral infusion (SIACI) of bevacizumab following disease progression after initial bevacizumab treatment and subsequent alternate clinical trial failure. There is a need to conduct further clinical trials to evaluate the benefits of rechallenge with SIACI versus IV bevacizumab for Glioblastoma, further exploring theories of bevacizumab resistance [4].

Some phase 2 trials had reported encouraging progression free survival with Bevacizumab in monotherapy or combined with chemotherapy in glioblastoma. However, phase 3 trials showed a significant improvement in progression free survival without a benefit in overall survival. To date, there are no predictive biomarker of response for Bevacizumab in glioblastoma [5]

There was interest in the role of bevacizumab, alone or in combination with cytotoxic drugs, but the results were conflicting [6] [7] [8] [9].

Given the highly vascular nature of Glioblastoma and its high expression of vascular endothelial growth factor and other angiogenic factors, recent investigation has turned to bevacizumab, an antivascular endothelial growth factor monoclonal antibody, for treatment of recurrent Glioblastoma. Phase 2 studies demonstrated the efficacy and safety of bevacizumab therapy for recurrent Glioblastoma, which led to its approval by the US Food and Drug Administration in 2009 for use in recurrent Glioblastoma. Since then, several new Phase 2 studies and retrospective series have demonstrated that bevacizumab significantly increased six-month progression-free survival in patients with recurrent Glioblastoma and may do so in new-onset Glioblastoma [10].

Further studies in recurrent disease are being conducted; preliminary results of a randomized trial showed favorable results with the combination with CCNU, and final results are awaited. Meanwhile, outside the realm of clinical trials, the current trend appears to be to reserve bevacizumab for use in recurrent disease, or for patients with moderate or severe neurologic symptoms, either in the newly diagnosed or recurrent setting. Further research efforts are needed to determine optimal candidates for this treatment from a molecular standpoint, as well as to develop imaging tools capable of accurately identifying response and progression, and to establish new drug combinations that could result in unquestionable clinical benefit and improved survival in these patients [11].

Monitoring response

In this setting, traditional anatomic MRI methods such as post-contrast T1-weighted and T2-weighted imaging are proving unreliable for monitoring response.

Standardized relative cerebral blood volume (rCBV) derived from dynamic susceptibility contrast MRI is predictive of overall survival (OS) and progression free survival (PFS) in patients with recurrent high-grade brain tumor treated with bevacizumab [12].

Overall survival

Trials on recurrent glioblastoma have shown that bevacizumab alone is able to increase response rate on MRI, median and 6-month progression-free survival (PFS), and modestly overall survival, allowing an improvement of neurological function and a reduction of steroids.

Any drug combination was not superior over bevacizumab alone. A synergistic effect of CCNU has been suggested when added to bevacizumab (BELOB trial), but excluded when added to cediranib (REGAL trial). Phase III trials on bevacizumab in newly diagnosed glioblastoma have shown an improvement of PFS of 3-4 months, but failed to prolong overall survival.

In a randomized trial of bevacizumab for newly diagnosed glioblastoma, the first-line use of bevacizumab did not improve overall survival. Progression-free survival was prolonged but did not reach the prespecified improvement target. (Funded by the National Cancer Institute; ClinicalTrials.gov number, NCT00884741.) [13].

Unexplained is the observation that females had longer overall survival (OS) with BEV than males in patients with progressive glioblastoma [14].

To overcome the limitations associated with using OS as the primary endpoint in studies involving new therapeutics, progression free survival (PFS) and objective response rate (ORR) should be considered important end points [15].

Timing of surgery and bevacizumab therapy

The optimum time between cessation of bevacizumab therapy and surgery was 4 weeks. The timing for reinitiation of bevacizumab postsurgery was at least 2 weeks. The duration of preoperative cessation of bevacizumab treatment is critical in preventing life threatening surgical complications. The interval between the surgery and reinitiation of bevacizumab can be shortened. However, more studies are needed to ascertain the exact timing of preoperative and postoperative therapy [16].

Case series

see Bevacizumab for recurrent glioblastoma case series.

Case reports

Bevacizumab for recurrent glioblastoma case reports.

References

1)
Friedman HS, Prados MD, Wen PY, Mikkelsen T, Schiff D, Abrey LE, Yung WK, Paleologos N, Nicholas MK, Jensen R, Vredenburgh J, Huang J, Zheng M, Cloughesy T. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. J Clin Oncol. 2009 Oct 1;27(28):4733-40. doi:

10.1200/JCO.2008.19.8721. Epub 2009 Aug 31. PubMed PMID: 19720927.
2)
Kreisl TN, Kim L, Moore K, Duic P, Royce C, Stroud I, Garren N, Mackey M, Butman JA, Camphausen K, Park J, Albert PS, Fine HA. Phase II trial of single-agent bevacizumab followed by bevacizumab plus irinotecan at tumor progression in recurrent glioblastoma. J Clin Oncol. 2009; 27:740–745
3)
Cohen MH, Shen YL, Keegan P, Pazdur R. FDA drug approval summary: bevacizumab (Avastin) as treatment of recurrent glioblastoma multiforme. Oncologist. 2009; 14:1131–1138
4)
Faltings L, Kulason KO, Patel NV, Wong T, Fralin S, Li M, Schneider JR, Filippi CG, Langer DJ, Ortiz R, Boockvar JA. Rechallenging Recurrent Glioblastoma with Intra-Arterial Bevacizumab with Blood Brain Barrier Disruption Results in Radiographic Response: a Case Report. World Neurosurg. 2019 Jul 24. pii: S1878-8750(19)32043-1. doi: 10.1016/j.wneu.2019.07.137. [Epub ahead of print] PubMed PMID: 31351210.
5)
Manneh Kopp RA, Sepúlveda-Sánchez JM, Ruano Y, Toldos O, Pérez Núñez A, Cantero D, Hilario A, Ramos A, de Velasco G, Sánchez-Gómez P, Hernández-Laín A. Correlation of radiological and immunochemical parameters with clinical outcome in patients with recurrent glioblastoma treated with Bevacizumab. Clin Transl Oncol. 2019 Mar 15. doi: 10.1007/s12094-019-02070-6. [Epub ahead of print] PubMed PMID: 30877636.
6)
Lombardi G, Zustovich F, Farina P, et al. Hypertension as a biomarker in patients with recurrent glioblastoma treated with antiangiogenic drugs: a single-center experience and a critical review of the literature. Anticancer Drugs. 2012;24(1):90–97.
7)
Reardon DA, Desjardins A, Peters KB, et al. Phase 2 study of carboplatin, irinotecan, and bevacizumab for recurrent glioblastoma after progression on bevacizumab therapy. Cancer. 2011;117(23):5351–5358.
8)
Zustovich F, Lombardi G, Pastorelli D, et al. Bevacizumab and glioblastomas, a single-centre experience: how disease history and characteristics may affect clinical outcome. Anticancer Research. 2010;30(12):5213–5216.
9)
Friedman HS, Prados MD, Wen PY, et al. Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma. Journal of Clinical Oncology. 2009;27(28):4733–4740.
10)
Hanson JA, Hsu FP, Jacob AT, Bota DA, Alexandru D. Antivascular endothelial growth factor antibody for treatment of glioblastoma multiforme. Perm J. 2013 Fall;17(4):68-74. doi: 10.7812/TPP/13-081. PubMed PMID: 24361023; PubMed Central PMCID: PMC3854812.
11)
Thomas AA, Omuro A. Current Role of Anti-Angiogenic Strategies for Glioblastoma. Curr Treat Options Oncol. 2014 Aug 31. [Epub ahead of print] PubMed PMID: 25173555.
12)
Schmainda KM, Prah M, Connelly J, Rand SD, Hoffman RG, Mueller W, Malkin MG. Dynamic-susceptibility contrast agent MRI measures of relative cerebral blood volume predict response to bevacizumab in recurrent high-grade glioma. Neuro Oncol. 2014 Jan 15. [Epub ahead of print] PubMed PMID: 24431219.
13)
Gilbert MR, Dignam JJ, Armstrong TS, Wefel JS, Blumenthal DT, Vogelbaum MA, Colman H, Chakravarti A, Pugh S, Won M, Jeraj R, Brown PD, Jaeckle KA, Schiff D, Stieber VW, Brachman DG, Werner-Wasik M, Tremont-Lukats IW, Sulman EP, Aldape KD, Curran WJ Jr, Mehta MP. A randomized trial of bevacizumab for newly diagnosed glioblastoma. N Engl J Med. 2014 Feb 20;370(8):699-708. doi:

10.1056/NEJMoa1308573. PubMed PMID: 24552317.

14) Levin VA, Mendelssohn ND, Chan J, Stovall MC, Peak SJ, Yee JL, Hui RL, Chen DM. Impact of bevacizumab administered dose on overall survival of patients with progressive glioblastoma. J Neurooncol. 2015 Jan 11. [Epub ahead of print] PubMed PMID: 25575937.

15) Lamborn KR, Yung WK, Chang SM, Wen PY, Cloughesy TF, DeAngelis LM, Robins HI, Lieberman FS, Fine HA, Fink KL, Junck L, Abrey L, Gilbert MR, Mehta M, Kuhn JG, Aldape KD, Hibberts J, Peterson PM, Prados MD; North American Brain Tumor Consortium. Progression-free survival: an important end point in evaluating therapy for recurrent high-grade gliomas. Neuro Oncol. 2008 Apr;10(2):162-70. doi: 10.1215/15228517-2007-062. Epub 2008 Mar 4. PubMed PMID: 18356283; PubMed Central PMCID: PMC2613818.

16) Abrams DA, Hanson JA, Brown JM, Hsu FP, Delashaw JB Jr, Bota DA. Timing of surgery and bevacizumab therapy in neurosurgical patients with recurrent high grade glioma. J Clin Neurosci. 2014 Dec 3. pii: S0967-5868(14)00562-1. doi: 10.1016/j.jocn.2014.05.054. [Epub ahead of print] Review. PubMed PMID: 25481268.