Is There a Role for Bevacizumab in the Treatment of Glioblastoma?

PRESENTATION OF THE CASE

A 54-year-old right-handed man presented with 3 months of progressively increasing frequency of partial seizures manifesting as olfactory hallucinations. Magnetic resonance imaging revealed a 3.5×2.5 cm heterogeneously enhancing mass within the right anterior temporal lobe and a 1-cm satellite lesion more posteriorly. Surgery was performed and the anterior lesion was completely resected; the satellite lesion was determined to be unresectable. Pathology results were consistent with a glioblastoma. An immunochemical stain for the IDH1 R132H mutant was negative and the O-6-methylguanine-DNA methyltransferase (MGMT) methylation status is pending. Is the addition of bevacizumab to this patient's treatment regimen warranted? *The Oncologist* 2013;18:1080–1082

PRO

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In 2009, bevacizumab gained accelerated approval from the U.S. Food and Drug Administration (FDA) for use as monotherapy in progressive glioblastoma, based on improved radiologic response rates observed with bevacizumab monotherapy in two single-arm or noncomparative phase II trials compared with historical data [1, 2]. The responses were independently determined to be 20% and 26% and were durable for approximately four months. On the heels of this approval, two multicenter, phase III, randomized, double-blind, placebo-controlled trials of bevacizumab in patients with newly diagnosed glioblastoma were launched: Radiation Therapy Oncology Group (RTOG) 0825 (NCT00884741) [3] and Roche-sponsored AVAglio (NCT00943826) [4]. Patients in both studies were randomly assigned to receive standard therapy (based on radiation and temozolomide) or standard therapy plus bevacizumab. The initial results of both trials were reported recently and have rekindled the debate regarding the efficacy of bevacizumab in glioblastoma [3, 4].

Overall survival (OS) and progression-free survival (PFS) were co-primary endpoints in both trials, and the outcomes of the two trials were similar. Bevacizumab did not improve OS in either study (median OS was 16–17 months for each arm in both studies); however, it increased median PFS to a similar degree in both studies (AVAglio: 10.6 vs. 6.2 months, hazard ratio [HR] 0.64, $p < .0001$; RTOG 0825: 10.7 vs. 7.3 months, HR 0.79, $p = .004$) [3, 4]. The PFS result in AVAglio was statistically significant [4], but the PFS result in the RTOG 0825 trial did not meet the prespecified significance level ($p = .002$) [3].

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CON

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Bevacizumab received accelerated approval from the FDA for use in first- or second-line treatment of recurrent glioblastoma based on two studies: one conducted by a small consortium of academic institutions and sponsored by Genentech (the BRAIN trial) and the second a monocentric trial from the National Institutes of Health (NIH) [1, 2]. Both trials purportedly demonstrated an improvement in objective radiographic response rate (20%–25%) and PFS (median: 4 months; PFS-6: 40%) when compared with historical trials using non-bevacizumab-based therapies. However, neither trial included a comparator agent such as lomustine. The BRAIN trial was a two-arm randomized phase II noncomparator trial of bevacizumab with or without irinotecan; whereas, the NIH trial was a single-arm phase II study of bevacizumab only [1, 2]. Regulatory agencies in Europe and Canada did not consider the trial results sufficiently compelling to approve bevacizumab for formulary use in recurrent glioblastoma, although the use of bevacizumab is commonplace in both regions. In addition, unlike for all other cancers in which bevacizumab is used, there has been no evidence to date of chemosynergy; that is, the augmentation of a chemotherapy regimen when used in conjunction with bevacizumab. In contrast, with recurrent glioblastoma, data have supported the use of single-agent bevacizumab only, as recently demonstrated in the Australian CABERET trial ($n = 122$), which compared bevacizumab with or without carboplatin and which found no difference in the two arms (PFS-6: 25%; median OS: 6.6 months), similar to the results of the BRAIN trial [3]. In the first trial to compare bevacizumab only with a comparator, the randomized phase 2 DUTCH BELOB trial allocated patients ($n = 153$) to bevacizumab versus lomustine versus the combination of be-

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The OS and mixed PFS results might suggest that bevacizumab does not have a role in newly diagnosed glioblastoma. However, there was significant crossover in both trials (~40% of those enrolled in RTOG 0825 and ~30% of those enrolled in AVAglio received bevacizumab at first progression), which may have been a confounding factor. Additionally, in AVAglio, the prolonged PFS appeared to be associated with a clinical benefit. Patients treated with bevacizumab remained functionally independent (Karnofsky performance status ≥ 70) longer (9 vs. 6 months) and had a longer time to deterioration of Karnofsky performance status (HR = 0.65, $p < .0001$) [4, 5]. Furthermore, those treated with bevacizumab went longer before corticosteroids were initiated (12.3 vs. 3.7 months, HR = 0.71, $p = .0018$) and a greater number of patients treated with bevacizumab who were already receiving corticosteroids were able to discontinue them (66% vs. 47%) [4, 5]. Disability and corticosteroid toxicity are frequent and often severe in patients with glioblastoma, and these results strongly suggest that bevacizumab may benefit some patients with newly diagnosed glioblastoma.

Clouding matters somewhat, however, the two trials had contradictory results in health-related quality of life (HRQoL) and neurocognitive outcomes studies. In the mandatory HRQoL studies in AVAglio, bevacizumab-treated patients experienced improved HRQoL [5], whereas bevacizumab-treated patients in the elective RTOG 0825 studies had greater decline in patient-reported HRQoL [6] and neurocognitive function [7]. The reasons for these discrepancies are unclear.

Is prolongation of PFS, greater maintenance of independence, and avoidance of corticosteroids enough to warrant upfront bevacizumab? Probably not for all patients. However, it remains to be determined whether bevacizumab is useful for certain subgroups of patients with glioblastoma. RTOG 0825 was unable to identify any sensitive clinical or molecular subgroup [3]. Notably, patients who had unresectable tumors (thus only had biopsy) were significantly under-represented in these trials because the availability of a significant amount of tissue for study was a requirement for enrollment in both studies (0% in RTOG 0825 and approximately 11% in AVAglio). Cerebral edema is an exceptionally difficult problem in patients with unresectable glioblastoma (~16%), particularly during radiation. Bevacizumab may be especially useful for this population because the anti-edema property of anti-vascular endothelial growth factor agents may be their most potent antitumor effect [8]. A recent small, single-arm phase II trial investigating bevacizumab plus temozolomide (without radiation) in patients with adult unresectable newly diagnosed glioblastoma reported a median survival of one year, which compared favorably with historical data (OS: 6–8 months) [9].

Although bevacizumab's role in newly diagnosed glioblastoma is uncertain, its effectiveness in the recurrent setting is compelling. Several phase II studies have reported improved 6-month PFS (PFS-6), a standard efficacy measure for trials of recurrent glioblastoma, in bevacizumab-containing arms compared with historical data. This includes the two phase II studies that led to bevacizumab's accelerated FDA approval (PFS-6: 30%–50%) [1, 2]. Although no comparative randomized, controlled trials of bevacizumab for treatment of recurrent glioblastoma have been published, a preliminary report of the Dutch BELOB randomized phase II trial suggested superior survival with bevacizumab plus lomustine. The BELOB trial randomly assigned patients to bevacizumab, lomustine, or bevacizumab plus lomustine at first recurrence of glioblastoma. PFS-6 was attained by

vacizumab plus lomustine [4]. Somewhat surprising was the study finding that there appeared to be no difference in the bevacizumab-only and lomustine-only arms with respect to PFS-6 (11% vs. 18%) or median OS (8 months in both arms), but the combination of bevacizumab plus lomustine resulted in the best outcome (41% PFS-6; 11 months OS). The findings of the BELOB trial raise two questions thought to have previously been answered: Is single-agent bevacizumab truly superior to lomustine, and is the combination of bevacizumab plus lomustine superior to either agent alone (suggesting chemosynergy, as seen in all other solid cancers treated with bevacizumab)? The findings of the Dutch study were reassessed in the recently completed randomized phase III European Organisation for Research and Treatment of Cancer (EORTC) trial 26101 comparing bevacizumab only with lomustine only and with combination therapy followed by crossover at progression. There is a strong possibility that the Dutch trial results will be recapitulated in the EORTC trial and suggest that single-agent bevacizumab is not superior to lomustine, a finding that would be transformative with respect to how recurrent glioblastoma is managed. If the results further suggest that the combination of bevacizumab plus lomustine is superior, this regimen will likely replace the current use of bevacizumab only and duplicate in glioblastoma the concept of chemosynergy.

Very recently, the preliminary results of RTOG 0825 ($n = 637$) and AVAglio ($n = 921$) were presented at the American Society of Clinical Oncology annual meeting [5, 6]. Both studies were randomized phase III trials comparing temozolomide-based chemoradiation followed by postradiation temozolomide with or without bevacizumab in patients newly diagnosed with glioblastoma. Both trials reported similar results, with an improvement in median PFS (approximately 6 months vs. 10 months) in the bevacizumab-containing arm and no OS advantage (approximately 16 months in both arms of both trials). These results indicate definitively that the use of bevacizumab in newly diagnosed glioblastoma has no clear advantage relative to standard temozolomide-based chemoradiation. In part, the failure of upfront bevacizumab may reflect that 30% of those in the AVAglio trial and 40% of those in the RTOG 0825 trial not initially treated with bevacizumab received bevacizumab at time of first disease progression. The results of RTOG 0825 and AVAglio were further confirmed in the French ANOCEF single-arm phase II trial of bevacizumab plus temozolomide in elderly patients with newly diagnosed glioblastoma. There was no improvement in OS when results were compared with those of an earlier ANOCEF trial in elderly patients with glioblastoma given temozolomide only [7]. A secondary substudy in RTOG 0825 assessed patient-reported ($n = 507$) outcomes using the The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30, the Functional Assessment of Cancer Therapy–Brain, and the MD Anderson symptom inventory in addition to a standardized neurocognitive assessment in patients prior to first relapse. The substudy demonstrated no difference in treatment arms [8, 9]. Overall, these three trials suggest no benefit of bevacizumab in the upfront treatment of glioblastoma, aside from an improvement in PFS (currently unclear as to clinical relevance), a decreased incidence of pseudoprogression (9.3% vs. 2.2%), and a decreased steroid requirement [10].

Finally, something that is not frequently assessed in glioma trials is whether bevacizumab therapy is cost-effective in patients with glioblastoma in light of the high cost of bevacizumab and the

41% of those who received bevacizumab plus lomustine versus 18% of those treated with bevacizumab as a single agent versus 11% of those treated with lomustine as a single agent (OS: 11 months for bevacizumab plus lomustine vs. 8 months for monotherapy arms) [10].

Ultimately, there is mounting evidence that bevacizumab is effective in recurrent glioblastoma. Early data suggest that ongoing comparative, randomized trials will validate the benefit in terms of PFS and OS. Current and future studies (including the ongoing EORTC 26101 phase III trial in recurrent glioblastoma) may identify chemotherapy combinations that result in even greater outcomes. The utility of bevacizumab in newly diagnosed disease appears limited; however, the discrepancy in PFS and HRQoL results in the recent phase III trials suggests more data may be needed. Identifying a subgroup of patients with newly diagnosed glioblastoma who derive benefit from bevacizumab will be critical to its future in this setting. On a global perspective, glioblastoma remains a debilitating disease, and therapeutic advances are still measured in months. Gains in terms of functional independence and corticosteroid limitation can be precious achievements in this population, and by these measures alone bevacizumab would represent an improvement in the therapy of patients with newly diagnosed glioblastoma.

DISCLOSURES

The author reports no financial relationships.

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requirement for intravenous therapy once every two weeks. There has not been an assessment of quality-adjusted life-year, a measure of disease burden that includes both quantity and quality of life lived regarding bevacizumab therapy in patients with either newly diagnosed or recurrent glioblastoma. Such an assessment is a common method used to determine cost-effectiveness of medical therapies, including cancer therapies, and it would be relevant for an agent such as bevacizumab.

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