Bevacizumab is an active agent for recurrent high-grade glioma, but do we need randomized controlled trials?

Patrick G. Morris

High-grade gliomas (HGGs), including glioblastoma, are a heterogeneous group of primary brain tumors, associated with devastating neurological sequelae and limited survival. In 2005, a randomized phase III study established postoperative radiotherapy and temozolomide as the standard of care for patients with resected, newly diagnosed glioblastoma. Despite this progress, almost all patients relapse and therapeutic options in the recurrent setting are limited. The optimum approach for recurrent HGG is challenging because of tumor resistance and the worsening performance status of the patients. As glioblastoma is a highly vascular tumor and has high levels of vascular endothelial growth factor, there has been interest in the use of the vascular endothelial growth factor targeting, monoclonal antibody bevacizumab. In a series of phase II studies, bevacizumab alone or with irinotecan showed improvements in tumor response, disease control, and survival compared with historical controls. These results led to the licensing of bevacizumab for glioblastoma in the USA, but a contrasting view was adopted by the European Medicines Agency, because of (deemed) modest response rates and lack of direct comparisons with other agents. Against this background, Gil and colleagues conducted a retrospective review of 130 patients with recurrent HGG treated with bevacizumab and irinotecan and showed an encouraging median progression-free survival of 5.1 months (95% confidence interval, 4.4–5.9) and a median overall survival of 9.0 months (95% confidence interval, 6.7–11.2), in agreement with other series. In this editorial, the context and implications of these results are discussed, with a particular focus on the possible need and design of randomized phase III trials. ***Anti-Cancer Drugs*** **23:579–583 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

Anti-Cancer Drugs 2012, **23**:579–583

Keywords: bevacizumab, biomarkers, glioblastoma, high-grade glioma, irinotecan, phase II trials, quality of life, randomized phase III trial, response assessment

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Received 12 February 2012 **Revised form accepted** 14 February 2012

Introduction

High-grade gliomas (HGGs) are a heterogenous group of primary brain tumors with devastating neurological sequelae and limited survival. These tumors include anaplastic gliomas (AG) such as anaplastic oligodendroglioma (grade III) and anaplastic astrocytoma (grade III) as well as glioblastoma (grade IV) [1]. As these tumors are rare, there are significant challenges in defining the optimum therapeutic strategy. First, tumor-related factors include biological diversity, innate resistance to therapy, lack of active agents, and challenges in drug delivery across the blood–brain barrier. Second, patient-related factors such as poor performance status and the requirement for antiepileptics and corticosteroids are potential barriers to conducting clinical trials. Despite these challenges, the European Organization for Research and Treatment of Cancer (EORTC) Brain Tumor and Radiotherapy Groups and the National Cancer Institute of Canada Clinical Trials Group successfully conducted a landmark randomized phase III study, which demonstrated that addition of the alkylating agent temozolomide to postoperative radiotherapy improved survival for patients with newly diagnosed glioblastoma [2]. This study highlighted the importance of cooperative groups in conducting trials for these rare diseases and proved that progress in disease control and survival was possible with innovative strategies.

Bevacizumab for high-grade gliomas

Despite this success, almost all patients with glioblastoma ultimately relapse after first-line therapy. In fact, in the EORTC trial, the median overall survival (OS) was only 14.6 months [95% confidence interval (CI), 13.2–16.8] with radiotherapy plus temozolomide. For patients with recurrent disease, the therapeutic challenges identified above are magnified, partly because of worsening performance status and greater tumor resistance. Therefore, the development of effective therapies in this setting is an important area of ongoing research. One potential approach is the use of drugs that focus on inhibition of angiogenesis. There is a strong biological rationale for this, as glioblastoma is a highly vascular tumor and is associated with high levels of vascular endothelial growth factor [3].

Bevacizumab is a monoclonal antibody that targets vascular endothelial growth factor and has demonstrated activity in combination with chemotherapy in patients with a variety of solid tumors, including cancers of the colon, lung, and breast [4–6]. However, the use of

0959-4973 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CAD.0b013e3283528847

bevacizumab may result in significant adverse events, including the risk of hemorrhage and venous thromboembolism, for which patients with primary brain tumors are thought to be at particular risk. Although these complications are often treatable, intratumoral hemorrhage in patients with brain tumors might be associated with greater morbidity and mortality than intratumoral hemorrhage at other sites. In fact, concerns about the risk of intracranial bleeding led, in part, to the exclusion of patients with primary and secondary brain tumors from most early clinical trials of bevacizumab. Ultimately, over time, the low incidence of serious hemorrhagic complications with angiogenesis inhibitors shifted the risk–benefit analysis in favor of conducting clinical trials with bevacizumab in patients with HGG [7].

To date, the use of bevacizumab for recurrent HGG has mainly been investigated in phase II clinical trials. In one such study, patients with progressive glioblastoma after previous radiation and temozolomide were treated with bevacizumab and the topoisomerase I inhibitor irinotecan using two dosing schedules [8]. In a combined analysis of 35 patients, this combination resulted in a 6-month progression-free survival (PFS-6) of 46% (95% CI, 32–66). Building on these results, Friedman *et al.* [9] conducted a randomized phase II trial of bevacizumab alone or in combination with irinotecan in 167 patients with recurrent glioblastoma. Again, when compared with historical controls, bevacizumab alone and bevacizumab with irinotecan yielded encouraging results (PFS-6 was 43 and 50%, respectively) [9]. In this study, the median progression-free survival (PFS) was 4.2 months (95% CI, 2.9–5.8) and 5.6 months (95% CI, 4.4–6.2) for the two regimens and the median OS was 9.2 months (95% CI, 8.2–10.7) and 8.7 months (95% CI, 7.8–10.9), respectively. Using the WHO response criteria, the objective response rates were 28 and 38% for single agent and combination therapy, respectively [10]. Furthermore, these regimens were well tolerated (grade ≥ 4 adverse events occurred in 46 and 66% patients receiving bevacizumab and combination therapy, respectively) and prior concerns about intracerebral hemorrhage did not materialize, occurring in only 2.4 and 3.8% patients in the two arms of the study. Interestingly, the study also showed that the use of bevacizumab was associated with a decline in corticosteroid use over time, which has been proposed as an indicator of improvements in quality of life [11]. In another phase II study, in which 48 patients with recurrent glioblastoma were treated with single-agent bevacizumab, followed by bevacizumab in combination with irinotecan on tumor progression, PFS-6 was 29% (95% CI, 18–48) [12]. The results of these studies led to the approval of bevacizumab for recurrent glioblastoma in the USA. However, a contrasting view was adopted by the European Medicines Agency, which did not approve bevacizumab for this indication, partly because of the relatively modest response rates obtained but also because the possible survival benefits of bevacizumab could not be established as direct comparisons with other treatments were lacking. Therefore, further data on the optimum use of bevacizumab for HGG are needed.

Large retrospective series of bevacizumab and irinotecan for recurrent high-grade gliomas

In the article that accompanies this editorial, Gil *et al.* [13] report on a retrospective experience from The Spanish Neuro-Oncology Research Group (GEINO) of the combination of bevacizumab and irinotecan for recurrent HGG. This was a relatively large series of 130 patients, Karnofsky Performance Status (KPS) 60 or more and disease progression after prior radiation and temozolomide, in which 72% of patients had glioblastoma. All patients provided signed consent for the compassionate use of bevacizumab. Between July 2006 and November 2009, patients received a median of eight infusions of bevacizumab (range, 1–39). The inclusion of patients from 13 different institutions again highlights the importance of collaborative group efforts for rare malignancies. Furthermore, the inclusion of 27 (21%) patients with KPS 60 and patients up to 78 years of age may better reflect real-world experiences with bevacizumab than prospective phase II trials with stricter eligibility criteria. In this study, the median PFS was 5.1 months (95% CI, 4.4–5.9) and the median OS was 9.0 months (95% CI, 6.7–11.2), which are both encouraging compared with historical controls. In fact, these results are strikingly consistent with the prior randomized phase II study (median PFS 5.6 months and median OS 8.7 months) [9]. The current study by Gil and colleagues yielded several other important findings. Response rates were assessed using the rigorous MacDonald criteria and were excellent: 56% (95% CI, 44.7–67) for glioblastoma and 68% (95% CI, 49.5–82.6) for AG [13]. Improvements in neurological state and KPS were shown in 49.2 and 45.2%, respectively, of symptomatic patients receiving bevacizumab and irinotecan. Finally, the safety profile of this combination was broadly consistent with published studies. Importantly, tumor hemorrhage occurred in only one (1%) patient and thromboembolic events occurred in seven (5%) patients, all of which resolved with anticoagulant therapy and discontinuation of treatment [13]. Hence, this study adds to an important and growing body of evidence in support of the use of bevacizumab in patients with recurrent HGG. This leads to the question, given the weight of this evidence, as to whether we need randomized phase III trials to confirm these benefits.

Do we need large randomized trials?

Randomized phase III trials represent the gold standard in drug development and provide the highest level of evidence in support of novel therapies. However, in certain situations, it has been argued that there is such

overwhelming evidence in support of a new therapy that a randomized study is unnecessary. Similarly, when there is no therapeutic alternatives, there are scenarios in which it has been argued that it might be unethical to conduct a placebo-controlled phase III study. In medical oncology, there are rare examples of agents with such favorable risk–benefit ratios that the activity in phase I and II studies was deemed sufficient for regulatory authorities to license general clinical use. Generally, these advances have occurred in rare diseases with carefully defined targets such as the use of imatinib for gastrointestinal stromal tumors and, more recently, the use of the BRAF inhibitor vemurafenib in BRAF-mutant metastatic melanoma [14,15]. The publication of seminal articles from early-phase studies of both these agents in a high-profile medical journal is indicative of the importance of these results as characterized by the scientific community. Critically, it is important to ask whether the magnitude of benefit with bevacizumab in recurrent HGG, relative to the associated risks, is similarly sufficient to waive the requirement for a randomized phase III study.

At first glance, the median PFS (5.1 months) and OS (9.0 months) obtained in the study by Gil *et al.* [13] are consistent with previous phase II studies and might be considered sufficient to warrant the broader use of bevacizumab. As a historical control, the authors cite a randomized placebo-controlled study of 222 patients with recurrent HGG, half of whom had received prior chemotherapy in which the use of an intraoperative biodegradable polymer impregnated with carmustine led to an increase in the median OS from ~5.3 to 7.2 months [16]. Furthermore, in the upfront (as opposed to the recurrent) setting, the median OS in the phase III EORTC study was only 14.6 months with radiotherapy plus temozolomide. In the study by Gil and colleagues, the median interval from the first brain tumor diagnosis to bevacizumab was 14.6 months (range, 2–166) and these patients had received a median of two (range, 1–5) previous lines of chemotherapy. Although this could be interpreted as evidence of the activity of bevacizumab in heavily pretreated patients, there are other possible explanations for the favorable PFS and OS obtained. First, glioblastoma is a heterogeneous disease and selection bias might have been a significant factor. Despite a lack of effective second-line therapies at that time, in 2005, the EORTC study of radiotherapy and temozolomide was associated with a 2-year OS rate of 26.5% (95% CI, 21.2–31.7) [2]. The fact that patients in the current report had already survived a median of 14.6 months (range, 2–166) before treatment with bevacizumab might reflect selection of patients with indolent biology or chemotherapy-sensitive disease. Second, modern surgical techniques, radiotherapy, and better imaging could have improved survival independent of the treatment administered such that the comparison of modern series with historic controls may not be reliable or valid. Finally, modern pathological analyses could result in reclassification of many tumors as glioblastoma (grade IV), which might have been labeled as AG (grade III) in the past. This is analogous to stage shift, as documented in solid tumors, by which reclassification of some tumors from grade III to IV results in tumors with more indolent biology being included as glioblastoma, resulting in an overall improved survived for the group of patients with glioblastoma (grade IV). For these reasons, survival in single-arm studies compared with historical controls should be interpreted with caution, a fact that is appropriately acknowledged by Gil *et al.* [13].

There are additional reasons for a cautious interpretation of these data. Although generally well tolerated, the combination of bevacizumab and irinotecan resulted in the deaths of five (4%) patients from possible toxicity, including from leukoencephalomalacia, intestinal perforation, and tumor hemorrhage (possibly related to bevacizumab). In the current study, KPS 80 or more and not taking corticosteroids at baseline were associated with better OS. However, the results from other studies are not consistent in this regard and these findings should be interpreted as hypothesis generating rather than used to select patients for bevacizumab therapy. A critical issue not addressed by the current study is what is the benefit of irinotecan? Response rates to single-agent irinotecan range from 0 to 17%, and this agent is associated with diarrhea and myelosuppression, which may be debilitating [17–20]. Unfortunately, the lack of direct comparisons of single-agent irinotecan, single-agent bevacizumab, and the combination in the published studies means that this issue remains unclear.

Challenges in clinical trial design

There are clearly similarities in the scenarios for targeted therapies such as imatinib, vemurafenib, and bevacizumab for the corresponding rare tumors, in which there is limited activity of standard chemotherapy. However, there are significant differences in these situations, which may explain the different positions of regulatory authorities in the USA and Europe with respect to bevacizumab for HGG. First, the interpretations of tumor response within the brain (and by extension PFS) are challenging. It has become increasingly clear that standard MRI measurements of tumor size, which involve measurements of contrast-enhancing tumor volume, are not appropriate in the setting of antiangiogenic drugs, because these agents generally stabilize the brain–blood barrier, leading to decreased gadolinium contrast extravasation [21]. It has been suggested that changes can be observed on MRI after a single dose of bevacizumab, irrespective of any benefit in terms of tumor control. The use of novel approaches, such as the MacDonald Criteria, in this regard is helpful, but limitations remain. Second, there is a lack of rigorous prospective data from the published clinical trials indicating that bevacizumab improves quality of life in unselected patients with recurrent HGG,

although there is support for this effect [11,22]. For example, in a single institution retrospective study of 44 patients, patients selected for bevacizumab-based therapy were more likely to maintain functional status and decrease their use of corticosteroids than patients who did not receive bevacizumab [22]. The study by Gil and colleagues also suggests possible improvements in performance status and neurological function with bevacizumab and irinotecan, but this must be interpreted with caution, given the retrospective nature of the study. Finally, unlike the situation with vemurafenib and imatinib, there is a lack of a distinct, measurable, molecular target for bevacizumab. To date, there are no validated biomarkers either within brain tumor tissue or serum to predict which patients are likely to benefit from this approach. For all these reasons, randomized phase III studies with bevacizumab in HGG are needed.

The optimum design of phase III studies with bevacizumab is challenging. In countries where bevacizumab is already clinically available, it is unlikely that a placebo-controlled study would be possible. Furthermore, the interpretation of MRI scans in patients receiving antiangiogenic agents is complex. Therefore, novel designs are needed for studies in the 21st century. In one such approach, a treatment could be compared with the 'treatment of physician choice'. This approach was recently adopted in a phase III study of the novel microtubule agent eribulin in metastatic breast cancer [23,24]. The advantage of this trial design is that it reflects the real-world practice and provides a practical assessment of the benefits of the new treatment. However, this design does not incorporate a placebo and is therefore subject to biases in determining PFS, which might be of particular concern in light of the effect of bevacizumab on contrast enhancement on MRI. In the case of eribulin, the primary endpoint of the study was OS, a relatively 'clean' study end-point. Similarly, the use of OS as an end-point when examining the use of bevacizumab in HGG is important.

Future research

There are several important, ongoing clinical trials examining the possible benefits of bevacizumab for HGG. The EORTC are recruiting patients with recurrent grade II and III glioma without evidence of 1p/19q codeletion into a randomized study examining the benefit of adding bevacizumab to temozolomide chemotherapy [25]. The primary end-point of this trial is OS at 1 year and, importantly, this study includes rigorous quality of life and neurocognitive assessments, as well as a large translational component to develop future biomarkers. In a second randomized study, the EORTC are conducting a study comparing bevacizumab, lomustine, and the combination in patients with recurrent glioblastoma [26]. This study will examine the optimum sequencing of bevacizumab and the possible benefits of continuation of bevacizumab beyond first progression, by investigating this agent after progression on lomustine and the upfront use of bevacizumab, followed by the addition of lomustine on progression. In another ongoing study, the MD Anderson Cancer Center is comparing bevacizumab 10 mg/kg with 'low-dose' bevacizumab 5 mg/kg with lomustine [27]. This study may help determine the optimum dose of bevacizumab for recurrent HGG, which is currently unknown. It is possible that the lower doses of bevacizumab might confer similar benefits, but improved tolerability to the currently accepted standard dose. The results of this trial might have major implications for healthcare economics. In the upfront setting, the ongoing Radiation Therapy Oncology Group is a randomized, double-blind, placebo-controlled study, which aims to assess the impact of adding bevacizumab to the standard radiotherapy and temozolomide [28]. The use of OS as the primary endpoint in these studies may help circumvent the issues of interpreting MRI scans in patients receiving bevacizumab. Similarly, the rigorous use of quality of life, neurocognitive assessments as well as the translational aspects is highly commendable to actually determine the benefits of bevacizumab in recurrent HGG. The support of these (and other) studies is very important to determine the optimum use of bevacizumab for recurrent HGG.

Conclusion

The study by Gil and colleagues, a large retrospective experience, demonstrates that bevacizumab and irinotecan represent an active regimen for HGG. However, the benefits of this approach can only truly be determined by randomized phase III trials. The substantial efforts of cooperative groups have demonstrated that randomized, multicenter, phase III trials (the gold standard) are feasible for patients with HGG. We should accept nothing less for our patients. The significant challenges facing researchers lie in optimizing the use of valuable resources in these studies, using novel designs, rigorous biomarkers, and quality-of-life correlatives. In the future, the results of such studies may provide a more accurate understanding of the benefits of antiangiogenic therapy for HGG and build on the therapeutic advances achieved to date.

Acknowledgements

Conflicts of interest

Patrick G. Morris has received honoraria from Eisai and is a consultant for Elsevier (*OncologyStat.com*).

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