Bevacizumab plus irinotecan improves both response and survival in patients with recurrent malignant glioma: a survival gain analysis

Tao Xu\textsuperscript{1}, Juxiang Chen\textsuperscript{1}, Yicheng Lu\textsuperscript{1}, Johannes E. A. Wolff\textsuperscript{2}

\textsuperscript{1}Department of Neurosurgery, Changzheng Hospital, Second Military Medical University, Shanghai, 200003, China

\textsuperscript{2}Departments of Pediatrics and Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, TX, USA

Corresponding author:

Juxiang Chen

Department of Neurosurgery

Changzheng Hospital

Second Military Medical University

Shanghai 200003, China

Tel: +86-21-81885673

Fax: +86-21-63586116

E-mail: juxiangchen@126.com

Keywords: Bevacizumab, Irinotecan, Malignant glioma, Chemotherapy

Abbreviated running title: Bevacizumab & irinotecan in recurrent HGG.
Abstract

Background Bevacizumab plus irinotecan is a new chemotherapy protocol increasingly used for recurrent malignant glioma. Results from phase II trials suggest this drug combination is beneficial to patients, but no conclusive comparisons between this and other treatment protocols have been published.

Methods We performed a survival gain meta-analysis of phase II studies to evaluate the efficacy and safety of bevacizumab plus irinotecan; to do this, we utilized a preexisting database from which the mean overall survival and response rate of patients could be predicted. Survival gain, which characterized the influence of treatment, was defined as the difference between observed and predicted mean overall survival. Response gain was calculated the same way.

Results Seven hundred and forty one cohorts were enrolled in the database. Among them, two hundred and eighty two cohorts were based on recurrent cases, mean reported median overall survival was 10.96 ± 8.4 months, and mean response rate was 18.9%. We found that compared with other treatment protocols, bevacizumab plus irinotecan largely improved response rates ($P = 0.00002$) and had a possible moderate effect on overall survival time ($P = 0.024$). Hemorrhage, thromboembolic complications, and gastrointestinal toxicities were the most frequently reported side effects.

Conclusion The combination of bevacizumab and irinotecan can improve outcome in patients with recurrent malignant glioma. Randomized controlled trials are recommended to confirm these results.
Introduction

High-grade glioma (HGG) is the most common brain tumor in adults, and the outcome of patients with HGG remains poor \(^1\). The standard of care for adult patients with glioblastoma is radiation and temozolomide \(^2\). However, this regimen yields median survival times of only 12 to 15 months for patients with newly diagnosed glioblastomas and only 2 to 5 years for patients with newly diagnosed anaplastic gliomas \(^3\). Once the tumors recur, the prognosis is even worse, with a median survival of only 3 to 9 months regardless of the treatment regimen \(^4,5\). Very few evidence-based treatment options are available for patients with recurrent disease, and treatment response for glioblastoma has generally been less than 20\%, with a 6-month progression-free survival (PFS) rate of less than 30\% \(^4,6\). Part of the problem in finding other effective treatment regimens is the variability of outcome data in HGG studies, which is at least in part caused by disease heterogeneity and differing eligibility criteria \(^7,8\).

Topoisomerase 1 inhibitors, such as irinotecan and topotecan, provide a viable treatment option for tumors resistant to temozolomide as the two classes of agents’ mechanisms of action and known mechanisms of resistance do not overlap \(^9\). In one analysis, irinotecan had activity against nonglioma malignancies, such as gastrointestinal malignancies \(^10\), and excellent penetration through the blood-brain barrier, suggesting it would be a good choice for recurrent HGG. However, as a single agent, irinotecan showed disappointing results in the treatment of recurrent malignant gliomas \(^11\).
Bevacizumab, the humanized monoclonal antibody against vascular endothelial growth factor (VEGF), has been approved by the U. S. Food and Drug Administration (FDA) for the treatment of colorectal, lung, and breast cancers. In May 2009, FDA has granted accelerated approval for single bevacizumab for use in patients with glioblastoma that has progressed despite previous therapy. Bevacizumab has generally been used in combination with cytotoxic agents. When bevacizumab and irinotecan were used in combination to treat HGG, the value is still not completely clear. The treatment response rates ranged from 28 to 86%, with a 6-month PFS ranging from 9.5 to 78.6%. With this large variation in outcome data, the question of this drug combination’s effectiveness remained open.

Recently, a phase II study survival gain meta-analysis was reported using novel mathematical methods to compare different nitrosourea drugs. Here we describe a second application of the same mathematical technology and its expansion to also analyze response to describe results from several phase II trials of bevacizumab and irinotecan for recurrent HGG.

**Materials and Methods**

Identification and selection of studies

This analysis was based upon a database that had been created for a treatment arm summarizing analysis by compiling information on HGGs from literature published from 1976 to 2008; this method generally falls under the umbrella of
The preexisting database had been expanded through May 2008.

For the question addressed by our study, a further independent search was carried out by querying the PubMed (updated through September 2009), EMBASE (1980-September 2009), and Cochrane controlled-trials registry databases using the search words “bevacizumab,” “irinotecan,” “CPT-11,” “glioma,” and “glioblastoma.” No language or date limitations were imposed. The following selection criteria were applied: (1) study population of patients with histologically proven malignant glioma, all of whom had experienced tumor progression that was measurable on magnetic resonance imaging (MRI) and received bevacizumab plus irinotecan as salvage chemotherapy; (2) study contained information on the diagnosis of recurrent malignant glioma, treatment protocol, criteria for response, responses to treatment, and overall survival or PFS; (3) in case of duplicate publication of the same patient cohort, only the most recent publication was used for further analysis. The decision to include a trial was made separately by two of our researchers (Xu and Chen), who then compared their lists and resolved any discrepancies.

Data extraction

As described before, the analysis was based upon a database. Briefly, a database with one line per patient cohort was generated. The median overall survival time was recorded from each study. Other outcome parameters and population characteristics were analyzed in relation to median overall survival and then used to
calculate predicted median overall survival using various multiple regression models; no treatment information was used in calculating the predicted overall survival and response. Finally, the predicted median overall survival was compared to the reported figure and the difference was called “survival gain”. Treatment protocols were evaluated by comparing patient cohorts with and without the treatment using a nonparametric test, such as the Mann-Whitney $U$ test.

Response was quantified in the meta-analysis in the same way as overall survival. The influence on response of parameters characterizing eligibility criteria and patient cohort was analyzed and used to compute the predicted response rate (complete response and partial response) of a given patient cohort. The “response gain” was then compared between groups.

The previously published method $^8$ was used with very minor modifications in the hierarchy of the various multiple regression models, as the ranking of prediction factors changed slightly. More important, compared with last version, the method was automated this time in SPSS syntax files using an updated version of the data analysis program, which will allow the database to be used by a broader spectrum of researchers. This also allowed us to easily repeat calculations when data entry or coding errors were detected. A total of 99 multiple regression models had been used for calculating the predicted overall survival, the predicted and observed median overall survival had a correlation of 0.542 ($P < 0.00001$). To validate this method, it had been used to calculate the predicted overall survival from the temozolomide studies and obtained the same results in last published paper $^8$. 

To analyze the effect of the combination of irinotecan and bevacizumab on median overall survival and treatment response, comparisons were made between cohorts treated with both drugs and those treated with neither. Histograms were created for visual comparison, and the Mann-Whitney $U$ test was applied when appropriate.

All analyses were done using SPSS software, version 16.0. (SPSS Inc® Fulfillment center Haverhill MA, SPSS 16.0)

**Results**

*Overall Survival of the database*

The database contained 547 cohorts between 1973 and 2008 when it was used in last published paper, with a mean reported median overall survival of all cohorts was 13.7 months (standard deviation [SD], 11.7 months)\(^8\). Now the database had been expanded from 547 to 741 cohorts, the mean reported median overall survival time goes to 13.7 months (SD 11.1 months) (Fig. 1). Among the 741 cohorts, 282 cohorts were based on recurrent cases, the mean of median survival time was 10.96 months (SD 8.4 months). The analysis of population characteristics that influenced median overall survival was repeated and gave essentially identical results as those reported previously\(^7,8\). At any given time points the overall survival rate was higher when the treatment was done as the fist-line therapy, the percentage
of glioblastoma patients was low, the percentage of completely resected tumors was high, the percentage of brainstem tumors was low, and the percentage of male patients was low. Treatment results were also better when radiation therapy was part of the treatment or multiple chemotherapy agents were used, but those treatment parameters were not used to create the various models, which were based exclusively on pretreatment parameters.

Response rates of the database

Among 326 cohorts that reported response rates, the mean response rate was 23.3% (range 0–100; see Fig. 2 for distribution). The response rate was significantly different when patients with newly diagnosed disease were compared with patients with recurrent disease (32.6% $\pm$ 23.4 versus 18.9% $\pm$ 20.5), when patients with glioblastoma only were compared with patients with anaplastic astrocytoma (18.2% $\pm$ 17.2 versus 30.8% $\pm$ 24.9), when a single-center study was compared with a multicenter study (29.8% $\pm$ 22.2 versus 13.4% $\pm$ 16.9), and the use of multiple chemotherapy as opposed to single agents (27.2% $\pm$ 23.7 versus 18.5% $\pm$ 19.7). No difference in response rates between studies done with children and those with adults was detectable. The initial Karnofsky score and gender did not seem to influence the response rate.

Description of studies with irinotecan and bevacizumab

A total of 12 studies finally met all our inclusion criteria, and 10 of the 12
studies were enrolled in the meta-analysis\textsuperscript{15-24}. The other two studies were excluded because of duplicate patient cohorts\textsuperscript{25, 26}. The basic characteristics of the enrolled cohorts are described in Table 1, and the treatment response was listed in Table 2.

Toxicity

Toxicity and side effects of bevacizumab plus irinotecan for patients with recurrent malignant glioma were reported in most of papers. Hemorrhage, thromboembolic complications (e.g., thrombotic thrombocytopenic purpura, deep venous thrombosis, pulmonary embolism, myocardial infarction), and gastrointestinal toxicities (e.g., diarrhea, gastrointestinal perforation) were most frequently reported. Further side effects included renal dysfunction (proteinuria, hematuria), fatigue, neutropenia, and others.

Comparing bevacizumab plus irinotecan outcome with other HGG data

We compared the response gain and survival gain between bevacizumab plus irinotecan cohorts (combination cohorts) and other treatment cohorts using the Mann-Whitney \textit{U} test. Since both newly diagnosed and recurrent cases were enrolled in the database, we first did the analysis in all patients, and then redid it only in recurrent cohorts.

Using the Mann-Whitney \textit{U} test, we compared the response gain of patients treated with the combination protocol to those treated with other protocols and came a clear result in favor of the novel drug combination: the mean rank of the 305
control cohorts was 153.96 while the mean rank of the 11 bevacizumab plus irinotecan cohorts analyzed was 284.27 ($P = 0.00003$). We then repeated the analysis in the recurrent cohorts, and found that: the mean rank of 186 control groups was 94.31, while the mean rank of 10 bevacizumab plus irinotecan cohorts was 178.27 ($P=0.00002$). These results showed that the improved response rate after treatment with the combination of irinotecan and bevacizumab was highly statistically significant. The response gain distributions of two groups are shown in Fig. 3.

Survival time was reported in 677 cohorts. In formal statistical testing of survival gain between patients treated with bevacizumab plus irinotecan and patients treated with other protocols, the Mann-Whitney $U$ test showed that the mean rank of the bevacizumab/irinotecan cohorts was 435.73 while the mean rank of control cohorts was 337.40; the $P$ value of 0.098 indicated that this survival gain difference was not statistically significant. When the analysis was redone only in the recurrent cohorts, we found that the mean rank of the 11 combination conhorts was 181.36, while the mean rank of 250 recurrent control cohorts was 128.78 ($P=0.024$). The response gain distributions of two groups are shown in Fig. 4. Progession free survival as additional endpoint was attempted but the data of the control group were insufficient for the comparison since PFS had been reported only rarely in the past (data not shown). In summary these results suggest that combination of bevacizumab and irinotecan can provide additional survival benefit comparing with other treatment protocol in recurrent HGG patients.
Discussion

The efficacy of bevacizumab plus irinotecan for recurrent malignant glioma has been evaluated in several clinical trials in recent years. However, the differences in patient characteristics made it difficult to judge the outcome results. Thus, we carried out this meta-analysis of the available evidence from phase II trials in order to more precisely define the combination’s efficacy. We found the treatment protocol can significantly improve both the response rate and survival time for patients with recurrent malignant glioma, these results were consistent with the experience of others.

Response rate and overall survival were considered the two most important parameters in assessing the efficacy of any treatment protocol, yet one of the two was necessarily only a surrogate parameter. Response rate was used in phase II studies as an endpoint because it was easy to evaluate in a short period of time, and it was hoped that treatment protocols which resulted in higher response rates will also resulted in higher survival rates in following phase III studies. This analysis adds clinical experiences showing the analogy-based prediction, to hold true only partially: while the benefit of the drug combination appeared large when considering response, the effect on overall survival was only marginal and detectable in a subgroup of patients only. However, response may translate directly into quality of life, and the fact that the two endpoints did not correlate strongly supported the response rate to be an important additional parameter in evaluating efficacy of treatment protocols.

Antiangiogenic treatment has been shown to have promising activity in the
treatment of recurrent malignant gliomas; so the Progression Free Survival time (PFS) was regarded as another important parameter for assessing efficacy of treatment protocols. Most bevacizumab plus irinotecan cohorts in our analysis used PFS as an endpoint. However, a recent study carried out by Norden et al found that PFS might not be an optimal endpoint for antiangiogenic treatment, because the use of contrast-enhancement MRI may overestimate the response rates. Anti-VEGF treatment can reduce vascular permeability, which can also account for the radiographic improvement; this may not necessarily reflect tumor cell death. Decreased enhancement could be because of both tumor cell death and the anti-VEGF effect; thus, a more precise radiological measurement for treatment response is needed. Chen et al reported F-fluorothymidine PET scanning could be an imaging biomarker used to predict overall survival in patients with recurrent gliomas who are treated with the combined bevacizumab and irinotecan protocol. Other possibilities for measuring response include the entire FLAIR signal abnormality in T2 weighted MRIs or nuclear medicine methods such as thallium, amino acids, or glucose. However, even with these measurements, the clinical relevance of these findings still remains a question.

Our finding that the response rate of an antiangiogenic treatment may result in additional survival benefit is consistent with previous phase II studies. However, Norden et al found that, compared to cytotoxic agents, antiangiogenic therapy may fail to prolong overall survival in patients with recurrent malignant glioma. It is also noteworthy that most patients died soon after disease progression when
bevacizumab failed, according to the discrepancies between PFS and overall survival benefits, indicating that heavily pretreated patients may develop VEGF-independent mechanisms of progression and must be closely monitored. 29

The role of irinotecan in the treatment regimen has been argued. 35 Single agent irinotecan used to treat patients with recurrent malignant glioma did not show good results, with response rates of 0–17% and 6-month PFS less than 25%. 11, 36 When irinotecan was added to bevacizumab, response rates and overall survival seemed to improve in phase II trials. The reason for this was still unclear; one possibility was that the use of bevacizumab could decrease interstitial pressure, improve tissue oxygenation, and increase delivery of irinotecan to the tumor. 37, 38 However, adding irinotecan to bevacizumab did not always result in improvement in overall survival time when compared with single-agent bevacizumab (overall survival, 8.9 months for combination and 9.7 months for single-agent). 39 In our study, we did not compare survival gain and response gain between single-agent and combined treatment because of insufficient data for patients with recurrent malignant glioma treated with single-agent bevacizumab. Further prospective studies may provide more evidence to determine the additional role of irinotecan in the treatment of recurrent malignant glioma.

The toxicity of this treatment protocol should also be considered. According to the clinical studies, hemorrhage, thromboembolic complications (thrombotic thrombocytopenic purpura, deep venous thrombosis, pulmonary embolism, myocardial infarction, etc.), and gastrointestinal toxicities were most frequently
reported (Table 3). Further side effects included renal dysfunction (proteinuria, hematuria), fatigue, neutropenia, and others. Vascular complications may be caused by the dose of bevacizumab. Compared with most studies that used the dose of 10mg/m² for bevacizumab, Bokstein et al used a dose of 5 mg/kg, which resulted in significantly lower vascular complication rates. The gastrointestinal side effects were mainly due to irinotecan; these side effects may decrease the quality of life in these patients and may even cause death.

The drug combination of irinotecan and bevacizumab resulted in response on radiological imaging which can translate into increased survival. Also, this drug combination had some moderate toxicity. The question as to how beneficial the drug combination is for a patient will thus depend on whether the patient experiences improved quality of life, which may result from the tumor shrinking or a decrease in brain edema adjacent to the tumor. Then the question becomes whether such improvement outweighs the loss of quality of life caused by drug toxicity. The answer to this question might be different for each patient. This might appear a quite small possible gain to be won and a complicated question to study. However, given the small steps of improvement in the treatment of HGG made over the past decades and the fact that improved response has rarely been shown with any these treatments, we feel it was worthy of study.

Our study also had some limitations. First, all included studies were phase II studies, It might bring great heterogeneity when there were no control group. Larger phase III randomized controlled studies compare bevacizumab plus irinotecan with
other treatment protocol are warranted so that the efficacy can be assessed properly. Second, the difference of survival gain between groups (p value of 0.024) might due to chance, although it was statistically significant. Compared with a p value of 0.00002 in response gain, it brought us the question whether the improved response really translated into a survival benefit for patients. The answer of this question might have to be answered in larger studies. Third, we didn’t include the PFS-gain because of insufficient data. Although the role of PFS in antiangiogenic treatment is still not clear, it’s a very important parameter to assess the efficacy of treatment protocols. It was used as an endpoint in all 11 bevacizumab plus irinotecan cohorts of 10 studies. However, it was not used widely in early studies. So it can not be calculated right now. Further analysis with more data might be helpful in this field.

In conclusion, our phase II survival gain meta-analysis showed the drug combination of bevacizumab and irinotecan might improve overall survival and response rate in patients with HGG. The final answer, how high the value of this drug combination is, will have to be given in a randomized study. Given the approval bevacizumab for recurrent glioma, the funding for such a study might need different sources than the pharmaceutical industry.

The author(s) declare that they have no competing interests

Tao Xu and Juxiang Chen carried out the search of studies, participated in the statistical analysis and drafted the manuscript. Yicheng Lu participated in the design of the study and revised the manuscript. J.E Wolff performed the statistical analysis,
participated in its design and coordination and helped to draft the manuscript. All authors read and approved the final manuscript.

**Acknowledgments** This study was supported by grants from the China 863 project 2007AA02Z483. We thank Ms Sue Moreau from M. D. Anderson Cancer Center for editing the paper.
Figure Legends

**Fig. 1** Observed median overall survival and percentage of 1-year overall survival for patients with malignant glioma in all published data.

**Fig. 2** Distribution of treatment response rates for patients with glioma in all published data.

**Fig. 3** Response gain distribution in control group (a) and bevacizumab plus irinotecan group (b), the combination of bevacizumab and irinotecan showed benefit in treatment response for patients with recurrent HGG.

**Fig. 4** Survival gain distribution in control group (a) and bevacizumab plus irinotecan group (b), the combination of bevacizumab and irinotecan showed benefit in survival time for patients with recurrent HGG.
Reference


Mean=23.2612
Std.Dev=22.30217
N=326

%Response (CR+PR)
CR=Complete Response; PR=Partial Response
Figure 4

(a) Histogram with Mean = 0.6437, Std.Dev. = 8.05165, N = 250

(b) Histogram with Mean = 2.9141, Std.Dev. = 5.03839, N = 11

Survival Gain
Additional files provided with this submission:

Additional file 1: tables09-10-18.doc, 63K
http://www.biomedcentral.com/imedia/1564039001332882/supp1.doc