Phase II Study of Bevacizumab Plus Irinotecan in Patients with Recurrent High-Grade Gliomas

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Abstract

Aim of the Study: This prospective phase II study was conducted to determine if the combination of a novel antiangiogenic therapy, bevacizumab, and a cytotoxic agent, irinotecan, is effective and safe for patients with recurrent high-grade gliomas.

Patients and Methods: Patients with recurrent high-grade gliomas were treated with bevacizumab 10mg/kg in combination with irinotecan. Patients taking enzyme-inducing antiepileptic drugs (EIAED) received irinotecan 340mg/m², whereas patients not taking EIAED received 125mg/m² i.v. The combination were given every 2 weeks until the occurrence of grade 3/4 toxicity or tumor progression. Tumor response and toxicity were assessed.

Results: The present study included 23 patients with recurrent high-grade gliomas (13 patients had grade IV glioma, and 10 patients had grade III glioma). The study was carried out in the Clinical Oncology Department, Ain-Shams University Specialized Hospital between February 2009 to August 2010. There were 15 males and 8 females, the median age was 44 years (range 26-62 years), with a median karnofsky performance status (KPS) of 80%. All patients had undergone prior surgical resection with radiation therapy and temozolomide. Out of the 23 patients, 11 patients (47.8%) achieved an objective response (partial response). All objective responses were evident on the first radiologic evaluation performed after the 4 initial treatments. Five patients (21.7%) had stable disease and 7 patients (30.4%) had disease progression. The patients who responded were able to taper their steroids and improved neurologically. The 6-month progression free survival (PFS) rate was 64.9% (CI: 44%-85.8%) and at 12 month was 58.4% (CI: 34.3%-82.6%). The 6-month overall survival (OS) rate was 65.2% (CI: 45.8%-84.7%) and at 12 month was 60.9% (CI: 38.3%-83.4%). When survival was analyzed according to the different prognostic factors, it was found that responders showed significantly better OS and PFS (p=0.032, 0.036 respectively). The 23 patients received 4-16 doses of treatment (median 8). Overall, patients tolerated treatment well. None of the patients discontinued treatment or had dose reduction because of side effects or poor compliance. Importantly, we did not observe any thrombotic complications or severe bleeding other than epistaxis in 2 patients (8.6%). There were no grade 3/4 hematologic toxicities included; 3 cases (13%) of fatigue and another 2 cases (8.6%) of hypertension.

Conclusions: The combination of bevacizumab and irinotecan is an active regimen for recurrent grade III-IV glioma with acceptable toxicity.

Key Words: High-Grade gliomas – Bevacizumab – Irinotecan.

Introduction

MALIGNANT gliomas, predominately glioblastoma multiforme (GBM), the most common histologic subtype, accounts for nearly 80% of all malignant brain tumors. They are characterized by diffuse parenchymal infiltration and prominent angiogenesis [1]. Even with the emergence of new therapies, current standard treatment for newly diagnosed patients with GBM receiving optimal surgical resection and chemoradiation results in a relatively poor median survival of only 14.6 months and a 2-year survival rate of 26% [2]. Key prognostic factors that influence outcome include tumor histology, functional performance status, age and extent of surgical resection [3].

The optimal treatment for patients with recurrent or progressive GBM is unclear, and there is no widely accepted standard of care. Several chemotherapeutic agents or biological agents may palliate patients, but the agents that have been used produce only minimal increases in survival [4]. Because the majority of patients fail to respond to temozolomide in the up-front or recurrent disease setting, clearly, new regimens are needed for the more formidable recurrent GBM. One approach has been to administer nitrosoureas, which are also alkylating agents, and for which the mechanisms of resistance are similar to those encountered with temozolomide therapy, particularly, the resistance enzyme 06- methylguanine-DNA methyltransferase (MGMT). As with single-agent temozolomide, nitrosoureas alone produce response rates of less than 10%, 6-month PFS rates of less than 20%, and median OS.
of 6 to 12 weeks [5]. However, nitrosoureas in combination with irinotecan have also produced similar, small increments in response rates (21.4%) and survival (6-month PFS 30.3%) [6].

The disappointing results of most therapeutic strategies in the setting of relapse have led to efforts to find more effective therapeutic approaches to target mechanisms that underlie glioma development and growth as well as better tolerated treatment options. The most promising of which appears to be the combination of irinotecan and the angiogenesis inhibitor bevacizumab [7].

Tumor angiogenesis plays a major role in tumor growth, invasion, and metastasis. Vascular endothelial growth factor (VEGF) is a major mediator of angiogenesis and is widely expressed in brain tumors especially malignant glioma. Increased VEGF expression has been associated with a poor prognosis. Preclinical studies have suggested that targeting VEGF function through neutralizing antibodies to VEGF can inhibit the growth of malignant glioma [8,9].

Bevacizumab, the humanized monoclonal antibody against VEGF has been approved by the U.S. Food and Drug Administration (FDA) for the treatment of colorectal, lung, and breast cancers [10,11]. Bevacizumab has generally been used in combination with cytotoxic agents. The combination of bevacizumab plus chemotherapy is expected to have a synergistic effect in tumor control [12]. One hypothesis supporting the use of an antiangiogenic agent with cytotoxic chemotherapy holds that by eliminating poorly perfused erratic tumor vasculature, perfusion is relatively normalized which leads to improved tissue oxygenation and, possibly, more efficient drug delivery [13]. A phase II randomized trial conducted by Cloughesy, et al. [14], studied patients treated with bevacizumab alone and in combination with irinotecan. Both groups reported an improved 6-month PFS rates (35.1% with bevacizumab alone and 50.2% in combination with irinotecan).

Irinotecan is a topoisomerase 1 inhibitor that passes through the blood-brain barrier with a different mechanism of action than that of alkylating agents such as temozolomide, providing a viable treatment option for tumors resistant to temozolomide since the mechanisms of action of these two classes of drugs and the known mechanisms of resistance do not overlap. In addition, topoisomerase 1 inhibitors are not affected by the resistance enzyme MGMT [15]. Irinotecan has some activity in patients with recurrent GBM, with response rates of 0% to 17% reported for several trials [16].

In a phase II trial of GBM patients treated with a fixed dose of irinotecan of 125mg/m^2, 15% of the patients had a confirmed partial response [17]. The trial included pharmacokinetic evaluations, which documented low concentrations of irinotecan and the active metabolite SN-38 in patients on enzyme-inducing antiepileptic drugs (EIAED) and corticosteroids, likely secondary to increased clearance due to these agents. In another phase II study, a fixed dose of 300mg/m^2 of irinotecan was administered every 3 weeks, and there was a similar, confirmed partial response rate of 14% [18].

A phase II clinical trial conducted by Vredenburgh, et al. [19] using bevacizumab in combination with irinotecan reported objective radiographic response in 63% of patients, a 6-month PFS of 38% and a 6-month OS of 72%. Another trial performed by Norden, et al. [20] also demonstrated favorable results with a 60% objective radiographic response rate and a 6-month PFS of 42 and 32% for patients with GBM and anaplastic astrocytoma (AA), respectively.

However, the value of combining bevacizumab with irinotecan to treat high grade glioma is still unclear [21]. The treatment response rates ranged from 28 to 86%, with a 6-month PFS rate ranging from 9.5% to 78.6%. With this large variation in outcome data the question of the effectiveness of this drug combination remains open [22].

This study was conducted to determine if the combination of a novel antiangiogenic therapy, bevacizumab, and a cytotoxic agent, irinotecan, is safe and effective for patients with recurrent high-grade glioma previously treated with radiation therapy and temozolomide. End points included; 6- and 12-month PFS and OS rates, objective response rate and drug toxicity profile.

**Patients and Methods**

**Patient characteristics:**

Adult patients aged ≥18 and <70 years with histologically proven diagnosis of a high-grade glioma (World Health Organization grade II, III) that was progressive or recurrent after radiation therapy and temozolomide were eligible for the study. Conditions required for entry into the study included the following: (a) measurable disease by contrast-enhanced magnetic resonance imaging (MRI); (b) Karnofsky performance status (KPS) ≥60%; and (c) life expectancy >2 months. Minimum permitted time intervals from prior treatments were 6 weeks for intracranial surgery, and 4 weeks for radiation therapy and chemotherapy unless there was unequivocal evidence of tumor progres-
sion after radiotherapy or chemotherapy. Full recovery from the effects of any earlier intervention was required. Other eligibility criteria included; adequate hematologic status (absolute neutrophil count > 1,500/uL; platelet count > 100,000/uL; hemoglobin > 9gm/dL), adequate renal function (serum creatinine < 1.5mg/dL), and adequate hepatic function (bilirubin < 1.5mg/dL; serum levels of aspartate aminotransferase < 1.5 the upper limit of normal).

Exclusion criteria included the following: (a) evidence of hemorrhage on the baseline MRI as were patients receiving anticoagulation therapy; (b) a prior malignancy; (c) previous treatment with irinotecan or bevacizumab; (d) a serious concurrent infection, illness, or medical condition; (e) females who were pregnant or nursing; and (f) any other condition that would compromise treatment with reasonable safety. Agreement to practice adequate birth control methods was required for fertile patients.

Treatment regimen:

The dose of irinotecan was determined based on antiepileptic use: Patients taking EIAED received irinotecan 340mg/m², whereas patients not taking EIAED received 125mg/m².

Irinotecan was administered over 90min. Bevacizumab was to be dosed at 10mg/kg, with the first dose administered over 90min. If the patient had no adverse reactions, the second dose was to be administered over 60min, and all subsequent doses were to be administered over 30min. The patients were required to have an absolute neutrophil count > 1,000/uL, platelets > 100,000/uL, bilirubin < 1.5mg/dL, aspartate aminotransferase < 2.5x normal, creatinine < 1.5x normal. Appropriate antiemetics were used. A clinically appropriate daily dose of a corticosteroid, such as dexamethasone, was determined for each patient before beginning the first cycle. The dose was required to have been stable for at least 7 days before treatment initiation, and efforts were made to maintain the same dose until the radiographic tumor measurement was done.

Treatment with the same doses of bevacizumab and irinotecan was repeated every 2 weeks until the occurrence of grade 3 or 4 toxicity or tumor progression. Patients were allowed a one-time 25% dose reduction of irinotecan for grade 3 or 4 gastrointestinal toxicity or grade 4 hematologic toxicity. Patients were removed from protocol treatment for any of the following events: Development of grade 2 or worse CNS hemorrhage or a second occurrence of grade 4 non-hematologic toxicity, disease progression; circumstances for which continued treatment could be detrimental to the health of a patient, or noncompliance.

Patient evaluations:

Evaluations done within 14 days of initiating therapy included a medical history, physical and neurologic examinations, vital signs, performance status determination, complete blood count with differential and platelet counts, blood coagulation variables (partial thromboplastin time), serum chemistry profile. Urine protein analysis tests all the patients had a gadolinium-enhanced MRI at baseline before starting the treatment. A contrast and a noncontrast brain MRI were done within 7 days of starting treatment and every 6 weeks after starting treatment. A complete blood count with differentials, chemistry panel was repeated every 2 weeks. Histories and physical examinations were repeated every 6 weeks. Toxicities were evaluated during each cycle and graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) Version 3.0 [23].

Treatment response evaluation:

Radiographic response. Radiographic response was measured by comparing each patient’s baseline MR imaging performed before the initiation of therapy and serial MR imaging performed every 6 weeks after starting therapy. Imaging response criteria were defined as follows: Partial response (PR) was determined if the contrasted images showed a greater than 50% decrease in the area of enhancement and vasogenic edema, provided that the patient was on a stable or decreased dose of dexamethasone and also was stable or improved clinically. Complete Response (CR), was determined by the resolution of all measurable abnormalities on the contrast images for any patient who was on a stable or decreased dexamethasone dose and also was stable and improved clinically. Progressive disease (PD), an increase in the degree of enhancement and vasogenic edema by at least 25%, appearance of a new lesion, or deterioration in the patient’s clinical status that was thought to be related to tumor progression. The patient was deemed to be stable if the criteria for a partial or complete response or tumor progression were not met.

Clinical response. Any subjective improvement in neurological function, cognition, speech, mobility, or ability to perform activities of daily living was considered a clinical response.

Survival analysis:

The collected data was revised, coded, tabulated and introduced to a PC using Statistical package
for Social Science (SPSS 15.0.1 for windows; SPSS Inc, Chicago, IL, 2001). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

- Kaplan-meier survival analysis: A descriptive procedure for examining the distribution of time-to-event variables. Overall Survival was measured from the date of entry into the study until death from any cause or last follow-up. Progression free survival was measured from the date of entry into the study until date of first evidence of disease progression.

- Log rank test examine the equality of survival times across groups. $p$-value: Level of significant; $p>0.05$: Non Significant (NS), $p<0.05$: Significant (S), $p<0.01$: Highly Significant (HS).

**Results**

The present study included 23 patients with recurrent high-grade gliomas (13 patients had WHO grade IV glioma, and 10 had WHO grade III glioma). The study was carried out in the Clinical Oncology Department, Ain-Shams University Specialized Hospital between February 2009 to August 2010. Patients Characteristics are summarized in (Table 1). There were 15 males and 8 females, and the median age was 44 years (range 26-62 years), with a median KPS of 80%. Every patient had undergone prior surgical resection and external beam radiation therapy with concurrent temozolomide followed by 6 months of temozolomide.

**Tumor response:**

All patients were available for response evaluation. Out of the 23 patients, 11 patients (47.8%) achieved an objective response, all were partial responders. In addition, 5 patients (21.7%) had stable disease and 7 patients (30.4%) failed to respond to treatment with disease progression (Table 2). All objective responses were evident on the first radiologic evaluation performed after the 4 initial treatments. Among the 13 patients with GBM, 7 patients (53.8%) had an objective responses (partial responses), 2 patients (15.4%) had stable disease and 4 patients (30.8%) had disease progression. Of the 10 patients with grade III gliomas, 4 patients (40%) had an objective responses (partial responses), 3 patients (30%) had stable disease, and 3 patients (30%) had disease progression. The patients who responded were able to taper their steroids and improved neurologically. Among 16 patients (69.5%) showing objective response or stable disease, in 5 patients (21.7%) with stable disease the dose of steroids was not changed before the first MRI evaluation, and in 11 additional patients (47.8%) with objective response it was decreased, Fig. (1).

**Survival analysis:**

The 6-month PFS rate was 64.9% (CI: 44%-85.8%) and at 12 month was 58.4% (CI: 34.3%-82.6%) for the entire group of patients. The 6-month OS rate was 65.2 % (CI: 45.8%-84.7%) and at 12 month was 60.9% (CI: 38.3%-83.4%). Nine of the 23 patients have died of tumor progression and 14 patients remain alive after 48 to 72 weeks from the time of enrollment. Figs. (2,3) is the Kaplan-Meier survival curves. When survival was analyzed according to the different prognostic factors, it was found that responders showed a significantly better OS and PFS rates ($p=0.032$ and $p=0.036$ respectively). Figs. (4,5).

**Treatment toxicity:**

The 23 patients received 4-16 doses of treatment (median 8). Overall, patients tolerated treatment well. None of the patients discontinued treatment because of side effects or poor compliance. Importantly, we did not observe any thrombotic complications or severe bleeding other than epistaxis in 2 (8.6%) patients. For safety purposes, we excluded patients who have required therapeutic anticoagulation. A noncontrast brain MRI was done within 7 days of starting treatment. The non-contrast T1 and T2 images showed that no patient had evidence of hemorrhage throughout the study.

There were no grade 3/4 hematologic toxicities. Three cases (13%) of transient grade 3 non-hematologic toxicities (severe fatigue) were reported. The third drug-related adverse event was hypertension in 2 patients (8.6%). All cases were ultimately controlled with antihypertensive medication, and no patient required removal from study or dose reduction for this toxicity. Side effects are summarized in (Table 3).

**Table (1):** Patient Characteristics (no= 23).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
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<td></td>
</tr>
<tr>
<td>Median (range)</td>
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<td>26-62</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15</td>
<td>65.2</td>
</tr>
<tr>
<td>Female</td>
<td>8</td>
<td>34.7</td>
</tr>
<tr>
<td><strong>Karnofsky performance status</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>60%</td>
<td>3</td>
<td>15</td>
</tr>
<tr>
<td>70-80%</td>
<td>12</td>
<td>52.1</td>
</tr>
<tr>
<td>90-100%</td>
<td>8</td>
<td>34.7</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glioblastoma multiforme</td>
<td>13</td>
<td>55</td>
</tr>
<tr>
<td>Anaplastic astrocytoma</td>
<td>10</td>
<td>45</td>
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</table>
Table (2): Tumor response among patients with recurrent high-grade glioma.

<table>
<thead>
<tr>
<th>Response</th>
<th>Glioblastoma multiforme</th>
<th>Anaplastic astrocytoma</th>
<th>Total</th>
<th>No.</th>
<th>% effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete response</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>100</td>
</tr>
<tr>
<td>Partial response</td>
<td>7</td>
<td>4</td>
<td>11</td>
<td>47.8</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>2</td>
<td>3</td>
<td>5</td>
<td>21.7</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>4</td>
<td>3</td>
<td>7</td>
<td>30.4</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>10</td>
<td>23</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

Table (3): Adverse Effects of 23 patients with recurrent high-grade glioma.

<table>
<thead>
<tr>
<th>Adverse effect</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombocytopenia</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>-</td>
</tr>
<tr>
<td>Epistaxis</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Hypertension</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nausea/Vomiting</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Table (4): Treatment response of bevacizumab plus irinotecan for patients with recurrent high-grade glioma.

<table>
<thead>
<tr>
<th>Study</th>
<th>No.</th>
<th>Median age (year)</th>
<th>Histology</th>
<th>mPFS</th>
<th>PFS 6-month (%)</th>
<th>mOS</th>
<th>OS 6-month (%)</th>
<th>Response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chen [29]</td>
<td>21</td>
<td>58</td>
<td>WHO IV 17</td>
<td>4</td>
<td>2.4</td>
<td>9.5</td>
<td>8.5</td>
<td>61.9</td>
</tr>
<tr>
<td>Vredenburgh [12]</td>
<td>35</td>
<td>48</td>
<td>WHO III 35</td>
<td>0</td>
<td>5.5</td>
<td>46</td>
<td>9.6</td>
<td>77</td>
</tr>
<tr>
<td>Bokstein [15]</td>
<td>20</td>
<td>56</td>
<td>WHO IV 17</td>
<td>3</td>
<td>4.2</td>
<td>25</td>
<td>7</td>
<td>55</td>
</tr>
<tr>
<td>Vredenburgh [19]</td>
<td>32</td>
<td>52</td>
<td>WHO IV 49</td>
<td>28</td>
<td>5.7</td>
<td>38%</td>
<td>10</td>
<td>72%</td>
</tr>
<tr>
<td>Ali [7]</td>
<td>13</td>
<td>53</td>
<td>WHO IV 13</td>
<td>0</td>
<td>5.5</td>
<td>46.2</td>
<td>6.2</td>
<td>53.85</td>
</tr>
<tr>
<td>Desjardins [39]</td>
<td>33</td>
<td>43</td>
<td>WHO IV 0</td>
<td>33</td>
<td>6.9</td>
<td>55</td>
<td>14.9</td>
<td>79</td>
</tr>
<tr>
<td>Kang [40]</td>
<td>27</td>
<td>46</td>
<td>WHO IV 12</td>
<td>15</td>
<td>5.1</td>
<td>45.8</td>
<td>12.6</td>
<td>84</td>
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<tr>
<td>Poulsen [38]</td>
<td>52</td>
<td>46</td>
<td>WHO IV 28</td>
<td>24</td>
<td>5</td>
<td>32.4</td>
<td>6.9</td>
<td>NR</td>
</tr>
<tr>
<td>Zuniga Cohort A [31]</td>
<td>14</td>
<td>51</td>
<td>WHO IV 0</td>
<td>14</td>
<td>13.4</td>
<td>78.6</td>
<td>NR</td>
<td>85.7</td>
</tr>
<tr>
<td>Zuniga Cohort B [31]</td>
<td>37</td>
<td>53</td>
<td>WHO IV 37</td>
<td>0</td>
<td>7.6</td>
<td>63.7</td>
<td>11.5</td>
<td>78</td>
</tr>
<tr>
<td>Friedman [21]</td>
<td>82</td>
<td>57</td>
<td>WHO IV 82</td>
<td>0</td>
<td>5.6</td>
<td>50.5</td>
<td>8.7</td>
<td>NR</td>
</tr>
</tbody>
</table>

mPFS = Median progression free survival, mOS = Median overall survival, Response rate (%) = Complete response (%) + partial response %, NR = Not Reported.

Fig. (1): Postcontrast coronal T1-weighted magnetic resonance scans in a 27-year-old patient with recurrent glioblastoma multiforme before (left) and after (right) 4 treatments with bevacizumab and irinotecan, showing an impressive reduction of tumor mass (partial response) and mass effect.
Response rate and OS are considered the two most important parameters in assessing the efficacy of any treatment protocol. It is anticipated that treatment protocols that result in higher response rates will also result in higher survival rates [22]. The PFS time was regarded as another important parameter for assessing efficacy of treatment protocols [25]. However, a study carried out by Norden, et al. [26] found that PFS might not be an optimal endpoint for anti-angiogenic 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 [27]. 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 [28].

Chen, et al. [29] reported that 18 F-fluorothymidine PET scanning could be used as an imaging biomarker 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. However, even with these measurements, the clinical relevance of these findings still remains a question [30,31].

However, in the current study the radiographic responses were associated with clinical improvement as reported by patients and showed on neurological examination. The decrease in vascular permeability may have additional benefits in decreased cerebral edema, but the durability of the responses suggests that our results are likely secondary to tumor reduction and not just bevacizumab affecting the blood-brain barrier. The fact that the responding patients had an improved PFS compared with the nonresponding patients \( (p=0.036) \), further corroborates that the responses were true tumor responses and not just a dexamethasone-like effect.

Xu, et al. [22] found that the response rate of an anti-angiogenic treatment may result in additional survival benefit and this was consistent with
previous phase II studies [14,22]. In the current study the responding patients had an improved OS compared with the nonresponding patients (p = 0.032). However, Norden, et al. [36] found that, compared to cytotoxic agents, antiangiogenic therapy may fail to prolong OS in patients with recurrent malignant glioma.

The differences in patient characteristics made it difficult to judge the outcome results [32]. Thus, Xu, et al. [22] carried out a meta-analysis of the available evidence from phase II trials in order to more precisely define the efficacy of the combination. About 411 patients were included in their analysis. They found the treatment protocol might improve both the response rate and survival time for patients with recurrent malignant glioma (Table 4). The median PFS time ranged from 2.4 to 13.4 months, the median OS time ranged from 6.2 to 14.9 months, with response rates ranging from 28% to 86%. Different doses of bevacizumab were used in these studies, but most patients received 10mg/kg, while some other patients received 5mg/kg, and 15mg/kg. The dose of irinotecan was mainly stable; most patients received 340mg/m² for those who take EIAED or 125mg/m² for those with non-EIAED.

In the current study all patients were available for response evaluation. Out of the 23 patients, 11 patients (47.8%) achieved an objective response, all were partial responses. In addition, 5 patients (21.7%) had stable disease and 7 patients (30.4%) failed to respond to treatment with disease progression. The rate of radiographic partial response 47.8% (11/23), and the rate of tumor control 69.5% (16/23) (PR+SD), were remarkable when compared to the 14% radiographic response rate and 39% tumor control reported in the meta-analysis by Wong, et al. [1], and were compare favorably to the phase II trial by Vredenburgh, et al. [19] who reported response rates of 63% and slightly inferior 6-month PFS (38% VS. 64.9%).

In the recent publication of Zuniga, et al. [31], no other treatment regimen for high-grade glioma has been shown to achieve such a high rate of response. Thirty-six out of 51 (70.5%) patients demonstrated partial 62.7% (32/51) or complete 7.8% (4/51) radiographic response to treatment and 8/51 (15.69%) remained stable. Median PFS was 9.5 months for the entire study population (95% CI = 6.5, 11.9), and the median OS was 13.4 months (95% CI = 10.3, 17.3) overall. In the present study the median PFS and the median OS were not reached. The mean OS was 13.1 month (95% CI = 10.6, 15.6) and the mean PFS was 11.2 month (95% CI = 7.7, 14.6).

Tumor recurrence in patients with inhibited angiogenesis may occur via cooption of normal vasculature and increased infiltration which can lead to new distant foci of enhancement. Zuniga, et al. [31] study results showed that 60.53% (23/38) of those who progressed demonstrated this distant pattern of recurrence on post contrast studies, with or without evidence of local progression. Seven patients (18.4%) showed progression on FLAIR without concordant findings on post-gadolinium MRI sequences.

A new set of guidelines for determining high-grade glioma response to therapy was published in 2010. This updated response assessment in neuro-oncology (RANO) criteria was the first revision to imaging response criteria for gliomas since 1990 and represents an international effort to standardize criteria for clinical trials [30]. Although this revision represents an important development, there are several promising imaging techniques on the horizon that will continue to improve our understanding of tumor biology. These imaging techniques include dynamic susceptibility contrast (DSC) MRI to measure cerebral blood volume (CBV), cerebral blood flow (CBF), and mean vessel density (MVD); dynamic contrast-enhanced (DCE) MRI to measure vascular permeability; diffusion MRI to measure tissue density; magnetic resonance spectroscopy to measure tumor metabolites; and a variety of PET tracers to measure different physiologic tumor processes [30].

The major concern of using this protocol in glioma patients is related to a relatively high previously reported complication rate [19]. In several meta-analyses, bevacizumab was reported to be associated with many side-effects, including venous thromboembolism [33], bleeding [34] and gastrointestinal perforation [35].

Zuniga, et al. [31] used the dose of 10mg/m² for bevacizumab and reported that six patients (11.7%) required discontinuation of treatment due to drug-related toxicity and complications, including one with end-stage renal failure and one with gastrointestinal perforation. Also Kreisl, et al. [36] found that amonge the 48 heavily pretreated patients that were accrued to their study, thromboembolic events (12.5%), hypertension (12.5%), and thrombocytopenia (6%) were the most common drug-associated adverse events. Six patients (12.5%) were removed from study for drug-associated toxicity (5 thromboembolic events, 1 bowel perforation).

A higher dose of bevacizumab may be responsible for vascular complications and a lower dose
of 5mg/kg every 2 weeks may result in the same efficacy but with a significantly lower (to none) complication rate [15]. The gastrointestinal side effects were mainly due to irinotecan; these side effects may decrease the quality of life in these patients [37] and may even cause death [38].

In the current study we did not observe any thrombotic complications or severe bleeding other than epistaxis. There were no grade 3/4 hematologic toxicities. Grade 3 non-hematologic toxicities included; 3 cases (13%) of fatigue and another 2 cases (8.6%) of hypertension.

Conclusions:

The combination of bevacizumab and irinotecan is an active regimen for recurrent grade III-IV glioma with acceptable toxicity. However, Larger phase III randomized controlled studies comparing bevacizumab plus irinotecan with other treatment protocols are warranted so that the efficacy can be assessed properly especially in the setting of newly diagnosed patients, where the largest effect on overall survival would be expected.

MRI and PET imaging of the brain have moved beyond anatomic imaging and are now capable of probing different aspects of tumor biology and response to treatment. These new techniques are increasingly being incorporated into clinical trials and even into clinical practice. Therefore, it is important to be familiar with the available imaging techniques and their potential uses versus limitations.

References


