Treatment With Bevacizumab and Irinotecan for Recurrent High-Grade Glial Tumors

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BACKGROUND. Response rates to second-line chemotherapy in recurrent high-grade glial tumors are low and new effective treatments are needed. The objective of this study was to evaluate response rates and tolerability of chemotherapy with bevacizumab and irinotecan in recurrent high-grade gliomas.

METHODS. Twenty patients with recurrent gliomas were treated with bevacizumab 5 mg/kg and irinotecan 125 mg/m² every 2 weeks. The response was evaluated by gadolinium-enhanced magnetic resonance imaging performed every 4 cycles of treatment.

RESULTS. The patients received 1 to 22 cycles of treatment. Nine of 19 patients available for response evaluation (47.3%) showed an objective radiologic response: 2 patients (10.5%) a complete response (CR), and 7 patients (36.8%) a partial response (PR). Two additional patients showed stable disease (SD) for 2 and 6 months, respectively. Eight patients developed rapid progression after 1 to 4 cycles of treatment. Median time to progression on treatment was 4.7 months. The 6-month progression-free survival (PFS) and overall survival (OS) were 25% and 55%, respectively. The adverse effects were mild and in all but 2 cases were no more than grade 2. There were no thrombotic complications or significant bleeding other than epistaxis.

CONCLUSIONS. The preliminary data show a promising high response rate of recurrent high-grade gliomas to chemotherapy with bevacizumab and irinotecan. The regimen is associated with minimal toxicity. Cancer 2008;112:2267–73. © 2008 American Cancer Society.

KEYWORDS: glioblastoma, high-grade gliomas, bevacizumab, irinotecan, toxicity.

Over the last 20 years dozens of antineoplastic agents have been tested as single agents and in different combinations for the treatment of high-grade gliomas. Despite this fact, treatment with cytotoxic chemotherapy has not significantly changed the dismal prognosis of these tumors. A meta-analysis of more than 3000 patients with high-grade gliomas treated in 12 randomized clinical trials demonstrated only a 6% increase in 1-year survival and a 2-month increase in median survival for patients treated with chemotherapy, as compared with patients receiving radiation treatment alone. Since 1980 the only Food and Drug Administration-approved drug for the treatment of malignant gliomas had been nitrosourea, joined only in the last decade by temozolomide and carmustine-polymer implantable wafers. Whereas concomitant use of radiation and temozolomide has been recently defined as the standard first-line approach for therapy of newly diagnosed grade 4 gliomas, the conventional treatment of recurrent high-grade glial tumors remains ill-defined. The use of second-line chemotherapy in this patient population is associated with unsatisfactory response rates of about 10% and median survival of less than 7 months.
New treatment strategies that include the use of ‘smart’ biologic agents gave rise to hopes in the last decade that this extremely poor outcome may be changed. Unfortunately, the results of most phase 2 clinical trials of new biologic agents have not shown significant improvement of response rates and survival for patients with recurrent high-grade gliomas.4–11

After the first preliminary report of an unusually high response rate of 43% to treatment with the combination of bevacizumab and irinotecan in a series of 21 patients with recurrent high-grade gliomas,12 this regimen has attracted considerable interest. In a recent publication of a phase 2 trial of this drug combination, the rate of radiographic response was 63%, with 6-month survival of 72%.13 Such a high response rate is highly unusual for this patient population. Unfortunately, 4 patients (12.5%) in this series suffered from severe thrombotic complications, resulting in 2 toxic deaths. Severe non-hematologic treatment-related side effects were reported as well in the initial publication of Stark-Vance,12 and included fatal intracranial hemorrhage in 1 patient and gastrointestinal perforation in another. We began using a similar treatment protocol in August 2005, with a reduced dose of bevacizumab as compared with the regimen of Vredenburgh et al.13 In this publication we report the results of treatment of 20 patients with recurrent high-grade gliomas who showed similar high rates of response, but without significant adverse effects of treatment.

MATERIALS AND METHODS

Twenty adult patients with recurrent high-grade gliomas were treated with irinotecan and bevacizumab in the Tel Aviv Sourasky Medical Center from August 2005 to April 2007. All patients signed informed consent, and we received approval by the Institutional Review Board for off-label use of irinotecan and bevacizumab. The patient characteristics are summarized in Table 1. There were 14 men and 6 women, with a median age of 56. Seventeen patients suffered from recurrent or progressive glioblastoma multiforme (GBM), and 3 other patients had grade 3 gliomas (anaplastic oligodendroglioma in 2 and anaplastic oligoastrocytoma in 1 patient). All patients had previously undergone 1 to 3 operations for removal of their tumors; all but 1 patient had been irradiated. All patients had received at least 1 line of prior chemotherapy; 13 patients had been initially treated according to the ‘Stupp regimen’.5 In 15 patients the treatment was started after failure of the previous chemotherapy protocol; in 1 patient after failure of radiation treatment; and in 4 patients within 1 month after surgery for recurrent tumor. We permitted treatment of patients with relatively low performance status (Karnofsky performance status [KPS] ≥50), providing that they had acceptable laboratory values. The median KPS for the group was 65%: 10 patients had KPS <70%, 7 patients had KPS 70% to 80%, and 3 additional patients had KPS 90% to 100%. We did not exclude patients with a history of thrombotic events or patients receiving chronic anticoagulation (patients taking warfarin were transferred to low molecular weight heparin).

<table>
<thead>
<tr>
<th>TABLE 1</th>
<th>Patient Characteristics</th>
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<tr>
<td>Characteristics</td>
<td>No. (Range)</td>
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<tr>
<td>No. of patients</td>
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<tr>
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<td>Anaplastic oligoastrocytoma</td>
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GBM indicates glioblastoma multiforme.

Treatment Regimen

On the basis of prior reports of increased metabolism of irinotecan in the presence of enzyme-inducing antiepileptic drugs (EIAED) via the cytochrome p450 hepatic pathway,14,15 these medications were discontinued before starting combination treatment, and patients were put on non-EIAED. Bevacizumab and irinotecan were administered intravenously every second week: bevacizumab at the dose of 5 mg/kg, and irinotecan at the dose of 125 mg/m². Blood count and urine protein analysis tests were performed before each treatment. Patients started the
protocol with a stable dose of corticosteroids and efforts were made not to increase the steroid dose before the first radiologic evaluation of response to treatment. Appropriate antiemetic drugs were permitted (including 20 mg of dexamethasone on day of treatment). A 25% dose reduction of irinotecan was permitted for patients with grade 3–4 gastrointestinal or grade 4 hematologic toxicity, but no patient required a dose reduction.

All the patients had a gadolinium-enhanced magnetic resonance imaging (MRI) at baseline before starting the treatment. Patients after recurrent surgery were permitted to start the treatment without radiologically measurable disease. MRI studies were performed every 4 treatments (2 months). Evaluation of response was performed according to McDonald et al. criteria. Patients without measurable enhancing disease postoperatively, who remained without measurable disease during their treatment course, were excluded from response evaluation.

Statistical Considerations
Because of the retrospective character of the study and lack of a suitable control group, comparative statistics were not performed. Survival analysis was done using Kaplan-Maier estimates for progression-free survival (PFS) and overall survival (OS).

RESULTS
The 20 patients received 1 to 22 cycles of treatment (median, 9.5). Treatment was continued until tumor progression in 17 patients. In 1 GBM patient treated postoperatively (described below), treatment was stopped electively after 8 months. In another patient with anaplastic oligodendrogloma treatment was stopped after 6 months of stable disease. Two patients continue the regimen at more than 16 months.

Nineteen of the 20 patients were available for response evaluation. Nine of 19 patients (47.4%) showed an objective radiologic response: 2 (10.5%) had a complete response (CR), and 7 patients (36.8%) had a partial response (PR) (Table 2). Notably, all objective responses were evident on the first radiologic evaluation performed after the 4 initial treatments. In 2 additional patients the disease remained radiologically and clinically stable (for 2 months in 1 patient and for 6 months in another). Remarkably, among 11 patients showing objective response or stable disease (SD) 1 patient did not receive steroids, in 2 patients the dose of steroids was not changed before the first MRI evaluation, and in 9 additional patients it was decreased. The clinical benefit of the treatment (CR + PR + SD) was 57.8%. Eight patients (42.1%) did not respond to treatment and showed signs of clinical progression, confirmed radiologically in 6 cases. Noteworthy, progressing patients received only 1 to 4 treatments, because the progression was evident early after starting the protocol.

We had only 1 case of a patient without measurable disease postoperatively at the time treatment was started. In this 28-year-old GBM patient, treatment was electively stopped, without evidence of active residual disease after 8 months (16 cycles). This patient was excluded from response evaluation. He developed a massive local recurrence only 2 months after the discontinuation of the treatment, underwent debulking of the recurrent tumor, and was again treated with the same regimen of bevacizumab and irinotecan. The patient did respond to treatment for a second time with a PR that unfortunately lasted only 3 months; he died 5.5 months after rechallenge with the regimen from progressive disease.

As mentioned above, radiologic evaluation of response was performed by a gadolinium-enhanced MRI every 4 treatments. Among responders, in 2 patients there was a decrease in enhancement on T1-weighted images without significant changes on fluid-attenuated inversion recovery (FLAIR) sequence, whereas 7 patients showed a decrease in both enhancement and FLAIR changes (Fig. 1). Radiologic progression or recurrence was diagnosed based on increasing enhancement in 4 previously responding or stable patients, and based on increased abnormal signal on both T1-weighted and FLAIR sequences in 6 patients (Table 3).
The 6-month PFS and OS for the whole group were 25% and 55%, respectively (Table 2). For responding patients (PR + CR) the 6-month PFS was 50%, and 6-month OS was 90%. The median PFS was 4.2 months (0.7–10.5 months) and median OS was 7.0 months (1.7–16.0 months). The Kaplan-Meier PFS and OS curves are shown in Figure 2.

Side effects are summarized in Table 4. Notably, there were no grade 3–4 hematologic toxicities, and only 2 cases of transient grade 3 nonhematologic toxicities (severe fatigue in 1 patient and psychosis in another), which did not require treatment discontinuation or dose reduction. We did not observe any thrombotic complications or severe bleeding other than epistaxis. None of the patients discontinued treatment because of side effects or poor compliance. Three responding patients remain on treatment 7 to 16+ months after initiation of treatment with the regimen.

**DISCUSSION**

Similar to previously published series, we observed an impressively high response rate of recurrent high-grade gliomas to a bevacizumab-based treatment protocol, with 2 of 19 complete responders and 7 of 19 partial responders. These results are particularly impressive, considering that the mean KPS in our group was 65% at the beginning of therapy, with 10 patients having KPS <70 (compared with...
mean KPS >80%, only 2 patients with KPS <70%, in the recent publication of Vredenburgh et al.\textsuperscript{13}). To our knowledge, no other treatment regimen for high-grade glioma has been shown to achieve such a high rate of response.

At this point it is not clear whether antiangiogenic mechanisms are more effective in the cases of enhancing measurable disease versus microscopic residual tumor. Theoretically, the antiangiogenic effect should work even more efficiently against microscopic disease where there is decreased tumor burden. One patient in our series began treatment postoperatively, without measurable disease, and appeared to have an extended disease-free interval (9.8 months), most likely as a positive response to this regimen. In the ongoing Radiation Therapy Oncology Group (RTOG) study 0625 for recurrent GBM, residual disease after surgery is not mandated for study eligibility.\textsuperscript{18}

Taking into account the possible influence of bevacizumab on blood-brain barrier permeability and vasogenic edema, the radiologic evaluation of response to bevacizumab-based therapy remains a challenge.\textsuperscript{17} By using standard MRI techniques we found that in most cases both response and progression can be demonstrated by changes on both gadolinium-enhanced T1-weighted images and on FLAIR images, whereas in a minority of patients alteration of enhancement without changes on FLAIR was evident. We have not seen patients showing only FLAIR improvement or deterioration, probably indicating that the primary target of treatment was enhancing tumor rather than infiltrative growth.

Irinotecan has been used for the treatment of malignant glial tumors both as a single agent\textsuperscript{19–21} and in combination with other cytotoxic drugs,\textsuperscript{22} but has shown only modest response rates and a marginal influence on PFS and OS. Presumably, the impressive therapeutic influence of the reported protocol in high-grade gliomas, like in other solid cancers, is because of a synergism between the cytotoxic agent (irinotecan) and the biologic antiangiogenic drug (bevacizumab).\textsuperscript{23} The major concern of using this protocol in glioma patients is related to a relatively high previously reported complication rate, including severe vascular thrombotic complications even resulting in toxic deaths.\textsuperscript{13} We propose that a higher dose of bevacizumab may be responsible for vascular complications and speculate that a lower dose of 5 mg/kg every 2 weeks may result in the same efficacy but with a significantly lower (to none) complication rate.

Clinical experience with bevacizumab includes several phase 1 studies that examined its pharmacokinetics and toxicity as a single agent\textsuperscript{24} and in combination with different cytotoxic regimens.\textsuperscript{25} Although no dose-limiting toxicity was reported at doses ranging from 3 to 20 mg/kg administered over different time schedules, the doses of 5 to 15 mg/kg every 2 to 3 weeks were arbitrarily chosen for most phase 2 clinical trials. Only a few dose-escalating phase 2 and 3 trials were performed aimed at estimating the optimal dose of the drug from the efficacy point of view.\textsuperscript{26–29} In a 3-arm randomized phase 2 trial, patients with advanced renal cell cancer were treated either with high-dose (10 mg/kg of bevacizumab every 2 weeks) or low-dose (3 mg/kg every 2 weeks) versus placebo.\textsuperscript{27} High dose of the drug was found to be significantly more effective in prolongation of median PFS as compared with low dose and placebo, although no additional intermediate doses between 3 and 10 mg/kg were examined. Another randomized phase 2 study evaluated safety and efficacy of bevacizumab combined with 5-fluorouracil and leucovorin (5FU/LV) in patients with metastatic colorectal cancer.\textsuperscript{28} Patients were randomized either to 5FU/LV alone or to a combination of 5FU/LV with low-dose bevacizumab (5 mg/kg every 2 weeks) or high-dose bevacizumab (10 mg/kg every 2 weeks). In this study the use of low-dose bevacizumab was associated with significantly better response rate and median time-to-progression, although thrombotic complications were reported in all 3 arms of the trial. According to the results of this study, the dose of 5 mg/kg every 2 weeks was selected for a major randomized phase 3 clinical trial of bevacizumab with irinotecan and 5FU/LV as a first-line treatment for metastatic colorectal cancer,\textsuperscript{30} and was approved as a standard chemotherapy regimen for this patient population. In a variety of clinical trials\textsuperscript{13,31–33} the dose of bevacizumab was chosen empirically and no dose escalation was performed.

In high-grade glial tumors the regimen initially used by Stark-Vance\textsuperscript{12} was a 6-week cycle, bevacizu-
mab 5 mg/kg every other week × 2, and irinotecan 125 mg/m² every week × 4, followed by a 2-week rest. In a recently published phase 2 study, both drugs were administered every other week on Days 1, 15, and 29 of a 6-week cycle. The dose of bevacizumab was 10 mg/kg and the dose of irinotecan (for patients not receiving EIAED) was 125 mg/m².

The mechanism of action and the pharmacologic effects of biologic agents differ significantly from classic cytotoxic drugs. The dose-response relation, valid for cytotoxic drugs, has not been proven as an appropriate mode for evaluating biologic agents, including bevacizumab. Typical phase 1 clinical studies, designed primarily to evaluate dose-limiting toxicities and maximal-tolerated dose (MTD) of drug, are probably not ideal for estimating the clinically optimal dose of drug for further clinical investigations of biological agents. Randomized dose-escalating phase 1–2 studies are a necessary step in clinical development of new biologic agents before proceeding to larger phase 3 trials.

In our descriptive series of patients with recurrent high-grade glial tumors, as compared with the results of Vredenburgh et al., a lower dose of bevacizumab (5 mg/kg every 2 weeks) has been shown to have comparable response rates and slightly inferior 6-month PFS (25% vs 38%), but is associated with significantly fewer vascular side effects. Similar results with the same dose of bevacizumab (5 mg/kg) were recently reported at the 2007 ASCO Annual Meeting. Although our series was not powered to show statistically significant survival benefits, the trends observed suggest consideration of alternative dosing of antiangiogenic agents in future studies. It may be that for biologic agents, bigger doses are not always better.

REFERENCES


