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ORIGINAL ARTICLE

Bevacizumab plus irinotecan in the treatment patients with progressive recurrent malignant brain tumours

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Abstract

Material and Methods. We retrospectively determined the efficacy and safety of a combination of bevacizumab and irinotecan in a consecutive series of 52 heavily pre-treated patients with recurrent high-grade brain tumours. Patients received bevacizumab (10 mg/kg) and irinotecan [340 mg/m^2 for those receiving enzyme-inducing antiepileptic drugs (EIAEDs) and 125 mg/m^2 for those not receiving EIAEDs] every 2 weeks. Fifty-two patients were included and 47 were evaluable for response. *Results.* Complete or partial response was observed in 25% of all cases (30% response in grade IV glioma and 15% in grade III glioma). Estimated median progression-free survival (PFS) for both grade IV and grade III glioma was 22 weeks. The 6-month PFS was 32% for all patients, 40% for grade IV glioma and 33% for grade III glioma. Estimated median overall survival was 30 weeks for all patients, 28 weeks for grade IV glioma and 32 weeks for grade III glioma. Four patients discontinued treatment because of unmanageable toxicity: cerebral haemorrhage, cardiac arrhythmia, intestinal perforation and diarrhoea, the latter resulting in death. *Discussion.* We conclude that the combination of bevacizumab and irinotecan shows acceptable safety and is a clinically relevant choice of therapy in heavily pre-treated patients with recurrent high-grade brain tumours.

Key Words: *Bevacizumab, Irinotecan, Glioma, recurrent, Treatment, Clinical trial*

Introduction

Treatment of patients with primary brain tumours is a multidisciplinary effort, consisting of maximal cyto-reductive surgery followed by radiotherapy and in some cases chemotherapy [1–3]. Patients with grade IV glioma can be treated with concomitant and adjuvant temozolomide, a regimen that has yielded a significant increase in survival [4]. Nonetheless, median survival remains <15 months and practically all patients eventually die from their disease [4]. The same holds true for grade III glioma patients, for which median survival is approximately 24 months [1]. At first recurrence, prognosis is even poorer with a median survival of 3–9 months, while at second recurrence, life expectancy drops to a few weeks for more than 90% of the patients [5,6]. These facts reflect the relatively poor efficacy of available chemotherapy and the scarcity of objective durable responses. Novel effective treatment modalities are therefore needed.

Malignant gliomas are highly vascular and often express abundant amounts of vascular endothelial growth factor (VEGF) [7]. VEGF stimulates/promotes tumour angiogenesis [8–11] but might also stimulate brain tumour stem cells [12] and decrease bioavailability of chemotherapeutic drugs [8–11]. Consequently, inhibition of VEGF activity may reduce angiogenesis, inhibit stem-cell proliferation, and increase the delivery and effect of cytotoxic chemotherapy [8,11]. Bevacizumab, a humanized monoclonal antibody that binds to and inhibits the activity of VEGF, has demonstrated synergy with

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cytotoxic chemotherapy in the treatment of various solid tumours, e.g., colorectal, lung, breast carcinoma [13–15]. Recently, promising results have been published showing durable responses using a combination of bevacizumab and irinotecan in patients with recurrent high-grade glioma [16–18].

Irinotecan, a topoisomerase I inhibitor, demonstrates excellent CNS penetration but has shown only modest efficacy in patients with recurrent primary brain tumours [3,19]. However, it is the only cytotoxic chemotherapeutic agent that has been administered in combination with bevacizumab to a substantial number of brain tumour patients. The toxicity of this combination has been shown to be manageable [16–18].

We therefore decided to conduct a clinical trial at our Danish centre, administering bevacizumab plus irinotecan to a consecutive series of heavily pretreated brain tumour patients with progression after standard primary and secondary treatment.

Patients and methods

The protocol was approved by The Danish National Board of Health and conducted in accordance with the Declaration of Helsinki. Patients provided signed, informed consent prior to enrolment. Patients had to be >18 years of age and have disease progression after standard treatment of histologically verified primary brain tumour according to WHO classification [20]. Histological diagnosis was based on the most recent surgical biopsy obtained before entering the study. Patients were required to have received at least one non-surgical treatment modality after recurrence. In addition, no other standard treatment was available.

Conditions for eligibility were as follows: measurable progressive disease by contrast-enhanced magnetic resonance imaging (MRI); WHO performance status 0–2; and a minimum of 6 weeks from prior surgery and 4 weeks from the prior chemotherapy. None of the patients received radiotherapy within 3 months of study treatment. Other inclusion criteria included: neutrophils $>3 \times 10^9$/L, haemoglobin >6.2 mmol/L, platelets $>125 \times 10^9$/L, serum ASAT or ALAT $<3 \times$ upper limit of normal (ULN), bilirubin $<1.5 \times$ ULN, and creatinine clearance >45 ml /min. Exclusion criteria included: a history of bleeding diathesis and coagulopathy; significant peripheral vascular disease; cardiac disease including acute myocardial infarction within 6 months; unstable angina pectoris; congestive heart failure; BP >150 /100 mmHg; proteinuria ≥grade 2; immunosuppressive co-medication other than corticosteroids; and any other active malignancy or condition preventing adequate follow-up or data collection.

Treatment

Bevacizumab and irinotecan were administered every 2 weeks and each cycle of treatment was defined as two treatment administrations. Bevacizumab 10 mg/kg was administered by slow IV infusion: over 90, 60 and 30 minutes for the first, second and subsequent doses, respectively. IV irinotecan [340 mg/m^2 for patients receiving enzyme-inducing antiepileptic drugs (EIAEDs) and 125 mg/m^2 for patients not receiving EIAEDs] was administered 60 minutes prior to bevacizumab. Atropine 1 mg SC was given 10 minutes prior to irinotecan to prevent cholinergic syndrome. For patients on corticosteroids, the dose had to be stable for >1 week before the first cycle of treatment. Before starting any treatment, haematological recovery was required as witnessed by ANC $>1.5 \times 10^9$/L and platelets $>100 \times 10^9$/L.

Dose modification was not allowed for bevacizumab. In case of unmanageable, bevacizumab-related side effects (grade 3 or 4 hypertension, venous thrombosis, haemorrhage, arterial thromboembolic event, grade 3 and 4 proteinuria and GI perforation), the patient discontinued study treatment. In case of grade 4 neutropenia or febrile neutropenia, the irinotecan dose was reduced to 80% of the starting dose. In case of grade 4 neutropenia after dose reduction, irinotecan was reduced to 60% of the starting dose. In the case of grade 3 or higher non-haematological toxicity, irinotecan dose was reduced to 80% of the initial dose in the following treatment cycles. Treatment was discontinued in the case of tumour progression, unmanageable grade 4 non-haematological toxicity or at the request of the patient. The physician could terminate study treatment if continuation was deemed unsafe.

Patient evaluation

A full medical history was determined before initiation of study treatment and all patients underwent baseline physical and neurological examination, performance status examination, routine laboratory tests (including blood chemistry and urinalysis) and MRI scans. Contrast and non-contrast MRI was repeated every 8 weeks during treatment, and clinical and laboratory tests every 2 weeks. Toxicity was evaluated according to NCI-CTCAE, version 3.0, criteria [21].

Treatment response evaluation

Response to therapy was evaluated using the MacDonald criteria [22], which comprises measurements of contrast-enhancing tumour size and recording the largest cross-sectional area of the

tumour, neurological status and steroid dose. A complete response (CR) was defined as complete disappearance of measurable disease by MRI, partial response (PR) as >50% reduction of MRI contrast-enhancing tumour, and progressive disease (PD) as a >25% increase in area of contrast enhancement. Patients, by definition, had stable disease (SD) if the criteria for CR, PR or PD were not met and no clinical progression was observed. Furthermore, we sub-defined a minimal response (MR) as a 25 to 49% reduction of MRI contrast enhancement. Patients with CR or PR also had to be taking the same or decreased steroid dose and have stable or improved neurological findings.

Results

Patient characteristics

The baseline demographic and clinical characteristics of the patients enrolled in the study are summarized in Table I. There were 34 males and 18 females. Twenty-seven patients had grade IV glioma, 13 had grade III glioma and five had grade III oligodendrogliomas. In addition, one patient had grade III ependymoma, one had grade III haemangiopericytoma; one had a malignant prolactinoma; three suffered from brain-stem gliomas and one had grade IV medulloblastoma.

All patients had received ≥2 treatment interventions before enrolment and most patients were heavily pre-treated with an average of two surgical interventions (range 1–4), usually at least two chemotherapy regimens (range 1–3) and radiotherapy. All patients had received standard primary treatment including surgery and radiotherapy with or without chemotherapy according to international recommendations [2,3]. At recurrence, most patients had received temozolomide as first-line treatment and some had received additional treatment with PCV (procarbazine, lomustine and vincristine), cisplatin, lomustine plus etoposide, or imatinib plus hydroxycarbamide depending on the local practice of the referring institutions.

Median age at enrolment was 46 (range 26–67) years. Time from primary diagnosis to enrolment ranged from 5 to 183 (median 37) months. This large range is primarily due to two factors: firstly, a number of patients who initially harboured a low-grade glioma presented malignant transformation when they were referred for the present treatment; and secondly, a number of patients had responded for a long time to previous therapy. As seen in Table I, patients with grade IV tumours had a significantly shorter median disease-free interval from primary diagnosis compared with patients who had grade III tumours. Eighteen of the 52 patients used EIAEDs. This group was statistically comparable to those not using EIAEDs and with respect to treatment response (data not shown). The reasons for patient discontinuation from the study and the duration of patients remaining on treatment are summarized in Table II.

Table I. Baseline patient demographic and clinical characteristics (N = 52)

Median age, years (range)	46 (26–67)
Gender	
Male	34
Female	18
WHO performance status	
0	20
1	21
2	11
Histological diagnosis	
Grade IV glioma (glioblastoma multiforme)	27
Grade III anaplastic astrocytoma	13
Grade III anaplastic oligodendroglioma	5
Grade III ependymoma	1
Grade III haemangiopericytoma	1
Malignant prolactinoma	1
Grade brain-stem glioma	3
Grade IV medulloblastoma	1
Concomitant medication	
EIAED	18
Non-EAIAD	15
No AEDs	19
Median time from primary diagnosis to enrolment, months1 (range)	
All patients	37 (5–183)
Grade IV glioma	16 (4–118)
Grade III glioma	47 (9–137)
No. of interventions before enrolment	
2	2
3	17
4	17
5	10
6	5
7	1
No. of responders (CR+PR) to previous chemotherapy	
All patients	8
Grade IV glioma	0
Grade III glioma	6
Others	2

Abbreviations: AED, antiepileptic drug; CR, complete response; EIAED, enzyme-inducing antiepileptic drug; non-EIAED, non-enzyme-inducing antiepileptic drug; PR, partial response.

Response

First response was evaluated after a minimum of 2 cycles of treatment and the best response was noted. Most patients had their best response after 2 to 4 cycles. For the intent-to-treat (ITT) population, response (CR+PR) was found in 13 of 52 patients (25%; 95% CI: 15–40%). Five patients

Table II. Reasons for patient discontinuation from the study and duration of study treatment

Reason for treatment discontinuation	Patients (no.)	Duration on study medication (months)
Disease progression		
Glioblastoma multiforme	12	2–12
Anaplastic Astrocytoma	7	2–14
Anaplastic oligodendroglioma	3	2–10
Other	2	2–6
Adverse events		
Grade 3 CNS haemorrhage	1	3
Grade 5 diarrhoea	1	1
Grade 3 intestinal perforation	1	4.5
Grade 3 cardiac arrhythmia	1	1
Toxicity and consent withdrawal	3	1–3

exhibited CR: four with grade IV glioma and one with grade III anaplastic oligodendroglioma.

For patients with grade IV tumours, response (CR+PR) was observed in 30% (95% CI: 14–57%) of those in the ITT population. Twenty-three of the 27 patients with grade IV tumours could be evaluated: results were 4 CR, 4 PR, 12 SD and 3 PD. Among the SD patients, six experienced MR, with shrinkage of initial contrast-enhancing tumour varying from 30 to 48%. Four grade IV patients could not be evaluated: one patient had clinical PD before evaluation; two patients did not want to continue participation in the study; and one patient died after the first treatment cycle due to unmanageable diarrhoea.

For the patients with grade III tumours, response was seen in three of 20 patients (15%; CI: 6–44%). One patient with grade III astrocytoma was not evaluable for response, because of discontinuation of treatment after 1 cycle of treatment. Among the patients with grade III astrocytoma, there were 2 PR, 9 SD and 1 PD. None of the grade III astrocytoma patients with SD could be sub-classified as MR. There was 1 CR and 4 SD among the five patients with grade III oligodendroglioma. There was 1 PR and 2 SD among the three patients with brain-stem glioma. The patient with prolactinoma experienced a PR. Each patient with grade III ependymoma and grade III haemangiopericytoma showed SD and the patient with grade IV medulloblastoma showed PD.

For the evaluable population, response (CR+PR) was observed in 13 of 47 patients (28%; 95% CI: 16–43%), while 20 of 47 patients had a greater than 25% radiographic response (43%; 95% CI: 29–58%). No correlation could be found between response to study treatment and response to prior radiotherapy or chemotherapy, disease duration before enrolment in the present study, performance status, or the use of steroids or antiepileptic drugs.

Table III summarizes change in steroid dose, WHO performance status and clinical symptoms according to best radiographic response in evaluable patients (N = 47). An improvement in or maintenance of steroid dose, performance status or clinical symptoms was almost invariable (80–100%) in patients with a clinical response (CR+PR), frequent in those with SD (59–96%) and uncommon in those with PD (0–60%).

Survival

Thirty-seven patients were followed for $\geq$6 months. In this population, progression-free survival at 6 months (6-month PFS) was 32.4% (95% CI: 18–49%). Corresponding 6–month PFS was 40% (95% CI: 16–67%) in 15 patients with grade IV glioma and 33.2% (95% CI: 18–67%) in 17 patients with grade III anaplastic glioma. Kaplan-Meier estimates showed median PFS as 22 weeks (95% CI: 16–28 weeks) in patients with grade IV glioma and 22 weeks (95% CI: 18–25 weeks) in patients grade III anaplastic glioma.

Median overall survival (OS) as estimated by Kaplan-Meier analysis was 30 weeks (95% CI: 24–37 weeks) in the total population. One- and 2-year survival was estimated to be 21% and 18%, respectively. Grade IV glioma patients had a median OS of 28 weeks (95% CI: 13–43 weeks) with 1- and 2 -year survival of 24% and 18%, respectively. Patients who responded (CR+PR) to study therapy had a median OS of 69 weeks (95% CI: 41–99 weeks) compared to 22 weeks (95% CI: 13–32 weeks) in patients with SD or PD. This difference is statistically significant ($p < 0.0001$, log-rank test). Grade III anaplastic glioma patients had an estimated OS of 32 weeks (95% CI: 25–39 weeks) and 1-year survival of 45%. There was no significant difference for OS between responders and non-responders ($p = 0.409$, log-rank test).

Safety

Study treatment was stopped because of toxicity in four patients: one each from grade 5 diarrhoea, grade 3 cerebral haemorrhage, grade 3 cardiac arrhythmia (atrial fibrillation) and grade 3 intestinal perforation. The GI perforation resulted from rupture of an anastomosis originating from a bowel resection performed 20 years prior to study treatment. Other grade 3 adverse events included:

Table III. Change in steroid dose, WHO performance status and clinical symptoms according to best radiological response in evaluable patients (N = 47).

	No. of patients (% improved or unchanged)					
	CR+PR (n = 13)		SD (n = 29)		PD (n = 5)	
Steroid dose						
Decreased	6	} 100%	14	} 96%	1	} 60%
Unchanged	4		8		2	
Increased	0		1		2	
NR*	3		6		0	
WHO performance status						
Improved	2	} 80%	0	} 59%	0	} 33%
Unchanged	6		13		1	
Worsened	2		9		2	
NR*	3		7		2	
Clinical symptoms†						
Improved	8	} 91%	13	} 81%	0	} 0%
Unchanged	2		8		0	
Worsened	1		5		5	
NR*	2		3		0	

*Data not recorded (not included in percent determination).
†Includes neurological symptoms, fatigue and/or mobility.
Abbreviations: CR, complete response; NR, not recorded; PD, progressive disease; PR, partial response; SD, stable disease.

superficial venous thrombosis (n = 1), hypertension (n = 3), neutropenia (n = 1), infection (n = 2) and proteinuria (n = 1). Most patients experienced grade 1 or 2 adverse events, which primarily consisted of neutropenia (21%), infections (14%), nausea and vomiting (33%), diarrhoea (34%), hypertension (11%), fatigue (56%), epistaxis (21%), proteinuria (56%) and increased transaminase values (28%). No difference in adverse events was observed between patients receiving EIAEDs and those not receiving EIAEDs (data not shown).

Discussion

This investigation represents a retrospective analysis of all patients with recurrent malignant brain tumours referred to our department for last-option treatment. We found that combination of bevacizumab and irinotecan induces a significant number of clinically relevant, durable responses (25% response rate). In addition, these responses translated into significant prolongation of survival. The response rate, with some complete responses (n = 5), and the improvement in 6-month PFS and OS compared with historical controls [5,6], was particularly encouraging**.** In most investigations using chemotherapy alone, response rates in recurrent high-grade glioma were approximately 5 to 20% and in heavily pre-treated patients, such as ours, 6-month PFS could be expected to be <10% [5]. We were particularly encouraged by the high CR rate among grade IV glioma patients (4 of 27; 15%) treated with bevacizumab+irinotecan in our series and the duration of response in these patients, as durable complete responses are extremely rare in this setting with previous treatment modalities. For example, Wong et al. [5] identified only one CR among 375 recurrent glioma patients (225 grade IV and 150 grade III) in pooled data from eight consecutive phase II clinical trials of chemotherapy.

Compared to other populations of patients with recurrent high-grade glioma treated with the combination of bevacizumab and irinotecan, our patient population is similar to that previously described by Stark-Vance [23], who found a response rate of 43% among 21 patients. Our data are comparable to the results for bevacizumab/irinotecan treatment in high-grade glioma patients [18] published by Norden et al. [18] and Guiu et al. [24], who showed response rates of 34% and 36%, respectively, with bevacizumab+irinotecan. However, our results were not comparable with those published by Vredenburgh et al. [16,17], who found response rates of approximately 60% for bevacizumab+irinotecan- our patient population was more heavily pre-treated. However, results of 6-month PFS and OS for grade IV gliomas are comparable to those published by Vredenburgh et al. [16,17]. It is possible that differences in MRI imaging evaluation or patient populations might explain these differences between studies. Our patients with grade III glioma did not show the response rates and the survival benefit reported by Vredenburgh et al. [16]. The reason for this is uncertain but may simply be related to non-comparable patient populations. However, it might also reflect a possible biological impact of

the significantly lower VEGF expression found in grade III as compared to grade IV tumours [25–28], which would make grade III tumours more likely to be less responsive to anti-VEGF therapy.

It has been argued that response rates to bevacizumab treatment using contrast-enhancement MRI scans might be overestimated [10,29]. Tumour blood vessels are leaky and bevacizumab regulates vascular permeability, probably by a transient normalization of tumour blood vessels. Consequently, targeting VEGF directly through bevacizumab may decrease leakage of the vessels resulting in decreased enhancement, although this does not necessarily reflect tumour cell death [8]. However, the responses that we and others have observed [16–18] resulted in clinical improvement and significantly prolonged survival compared with best supportive care [3]. This indicates that decreased enhancement was due to clonogenic tumour cell death, rather than a steroid-like effect. This conclusion is furthermore supported by a recent study by Chen et al. [30], who showed that a reduction in metabolic activity, as measured by ^{18}F-fluorothymidine PET scanning, correlated with response and survival in grade III and IV gliomas treated with bevacizumab plus irinotecan. Furthermore, we found that radiographic response in our patients was correlated with factors related to quality of life such clinical/neurological symptoms, WHO performance status and steroid dose.

Published response rates of irinotecan alone in patients with recurrent high-grade glioma are up to 15% [19] and studies using other anti-angiogenic agents such as thalidomide or vatalanib alone showed response rates of 6 to 9% [31–33]. Furthermore, these studies showed shorter median PFS and OS than in our study. In high-grade glioma patients, treatment with thalidomide plus temozolomide [34–36] or carmustine [37] produced response rates of 7 to 24% at first recurrence**.** However the combination of thalidomide and carmustine yielded a median PFS of just 14 weeks [37], which is less than we observed. It should be emphasized, however, that all the cited studies are small and other differences between patient populations might possibly explain some of the similarities and differences in efficacy. When responses did occur in these studies [19,31–37], they were almost invariably partial responses, with only the rare, isolated complete response

It appears that the combination of bevacizumab and irinotecan has at least an additive effect. While the reasons for this are still under investigation [9–11], several pathophysiological and non-pathophysiological factors have been proposed. The combination of the two drugs may increase apoptosis and decrease the number of tumour stem cells, decrease interstitial tissue pressure and normalize the tumour vasculature. The latter would increase irinotecan penetration into the tumour and all these mechanisms would facilitate increased tumour cell death [8,9,12].

We found that the safety of the combination of bevacizumab and irinotecan was acceptable. Adverse events were manageable in most cases. There was one treatment-related death (diarrhoea), a well known side effect of irinotecan [38]. There was a suggestion of increased risk of thromboembolic effects including one case each of cerebral haemorrhage, intestinal perforation and superficial venous thrombosis, which may have been related to and have been associated with bevacizumab [39]. With respect to cerebral haemorrhage, however, it should be noted that high-grade gliomas have a particularly high propensity to present with haemorrhage, up to 29% of patients with mixed oligodendroglioma/astrocytoma in a retrospective clinico-pathological review of consecutive brain tumour cases [40].

In conclusion, heavily pre-treated patients with recurrent high-grade gliomas show clinically relevant durable responses, with a substantial number of complete responses. We recommend that bevacizumab and irinotecan be offered to patients with recurrent grade IV tumours and be considered in future protocols for treatment of grade IV gliomas, including the first-line setting.

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