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ORIGINAL ARTICLE

Clinical outcome with bevacizumab in patients with recurrent high-grade glioma treated outside clinical trials

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Abstract

Background. Patients with recurrent high-grade glioma (HGG) have a poor prognosis and there is no defined standard of care. High levels of vascular endothelial growth factor (VEGF) expressed in HGG make the anti-VEGF monoclonal antibody bevacizumab (BEV) of particular interest. *Patients and methods.* In an ongoing registry data were collected from patients who have received BEV for the treatment of recurrent HGG. The primary objective was the identification of any clinical benefit as assessed by change in Karnofsky Performance Score (KPS), decreased steroid use and duration of treatment. *Results.* Two hundred and twenty-five patients with HGG were included (176 glioblastoma; 49 anaplastic glioma; median age 52 years). KPS improved in 10% of patients and remained stable in 68%. Steroids were stopped in 37.6% of patients. Median duration of treatment was 5.5 months; 19.1% of patients were treated for more than 12 months. Median overall survival from beginning of BEV treatment was 8.5 months. At the time of analysis, 169 patients (75.1%) had died and 56 patients (24.9%) were alive. Only 21 patients (9.3%) discontinued treatment due to toxicity. *Conclusions*. Our data reveal valuable palliation with preservation of KPS and an option for steroid withdrawal in patients treated with BEV, supporting the role of this therapy in late-stage disease.

High-grade gliomas (HGG) account for approximately 23.9% of all primary brain and central nervous system tumours and have an annual incidence rate of 5–7 cases per 100 000 population. The most common type of HGG is glioblastoma (WHO grade IV), accounting for approximately 53.8% of all gliomas [1].

Glioblastoma is associated with poor prognosis, with patients displaying a median survival of 15 months only when treated with current standard of care, involving maximal safe surgical resection followed by radiotherapy with concomitant and adjuvant temozolomide (TMZ) and individual therapy at recurrence [2,3].

Regardless of initial treatment, recurrence of HGG is inevitable. A variety of therapies have been investigated for patients with recurrent disease. According to the NCCN guidelines (www.nccn.org), patients can be offered drugs such as TMZ, nitrosoureas, PCV (procarbazine, CCNU and vincristine), cyclophosphamide, platinum-based regimens or bevacizumab (BEV; Avastin®, Genentech/Roche, Switzerland) alone or in combination with chemotherapy. Second surgery, second courses of radiation therapy and experimental treatment options are also offered at some centres. An overview by the North American Brain Tumour Consortium (NABTC)

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examined data from 596 patients (159 patients with grade III tumours and 437 patients with grade IV tumours) enrolled in phase II trials for recurrent HGG. Median survival durations, measured from time of registration, were 39 weeks (8.9 months) and 30 weeks (6.9 months) for grade III and grade IV tumours, respectively (Table I) [4].

To date, there is no established standard of care for patients with recurrent HGG. Salvage treatment remains palliative and should therefore meet palliative needs. High levels of vascular endothelial growth factor (VEGF) expression found in HGG [5] have made the VEGF monoclonal antibody BEV of particular interest in therapeutic strategies, both as an adjunct to radiotherapy [6] and in combination with chemotherapy, initially with irinotecan in analogy to previous experiences in colorectal cancer [7–9].

In 2009, the US Food and Drug Administration (FDA) and Swissmedic granted accelerated approval of BEV for the treatment of recurrent glioblastoma, whereas there is currently no such approval in the European Union [10]. The FDA and Swissmedic approval of BEV in recurrent glioblastoma is mainly based on data from two uncontrolled phase II trials [11,12]. The only randomised phase II trial was an open-label, non-comparative, multi-centre trial of BEV alone and in combination with irinotecan in 167 recurrent glioblastoma patients. Median progression-free survival (PFS) was 4.2 months (BEV alone) and 5.6 months (BEV with irinotecan). Median overall survival (OS) was 9.2 months (BEV alone; 95% CI, 8.2–10.7) and 8.7 months (BEV with irinotecan; 95% CI, 7.8–10.9) [11]. The second phase II trial, a single-centre study, investigated single-agent BEV followed by BEV plus irinotecan in 48 heavily pretreated patients with recurrent glioblastoma. Median PFS was 16 weeks (3.7 months) and median OS was 31 weeks (7.1 months) [12].

Outside of clinical trials, BEV-based regimens are now widely used in several countries where the drug is reimbursed for recurrent malignant glioma.

Our ongoing registry aims at addressing clinical outcome of BEV-based treatment in recurrent HGG after one or multiple prior therapies, using community-based data from patients treated at 30 centres in Switzerland, Austria and Germany.

Methods

In an ongoing and regularly updated registry (starting in August 2006), data on patient characteristics are collected from unselected patients with recurrent HGG treated at 30 centres in Switzerland, Austria and Germany. The decision to treat a patient with recurrent HGG with a BEV-based regimen and the frequency of treatment assessment either radiologically or clinically is the treating physician's choice. Patients are registered at the time of first BEV application, follow-up is until death.

Anonymous data are sampled using an institutional review board-approved written questionnaire. Baseline patient characteristics, medical history regarding the course of HGG, prior treatment regimens and patient outcomes focusing on BEV treatment are recorded.

The main objective of this analysis was the identification of clinical benefit as assessed by change in Karnofsky Performance Score (KPS; baseline KPS and best KPS during BEV-based treatment) and steroid use, as well as duration of treatment. We partitioned KPS into three groups and defined group I as good to excellent (KPS 80–100%) group II as moderate (KPS 60–80%) and group III as poor (KPS $< 60\%$). OS from start of BEV treatment is also of interest; other parameters include reasons for BEV discontinuation and safety. Response rates are not assessed in this cohort due to concerns

Table I. Common treatment regimens for recurrent glioblastomas.

	NABTC Phase II [4]	TMZ 7/7 [16]	CCNU [15]	BEV [11]	BEV/ CPT-11 [11]
Number of patients (n)	437*	64*	92	85	82
Median age (years)	52 (21–84)	51	55.3	54 (23–78)	57 (23–78)
KPS (%)					
90–100	40	72	49	44.7	37.8
70–80	54	–	50	55.3	62.2
In first relapse (%)	50	–	77	81.2	80.5
Time from diagnosis to treatment (months)	–	8.5	12	8.6	9.8
Median duration of response (months)	–	–	2.8–9.6	5.6	4.3
Median PFS (months)	1.6/3.4**	5.5	1.64	4.2	5.6
Median OS (months)	6/7**	8.7	7.1	9.2	8.7

*Patient cohort with grade IV tumors; **Non-temozolomide/temozolomide regimen, respectively.
NABTC, North American Brain Tumor Consortium; TMZ 7/7 temozolomide one week on, one week off; CCNU, lomustine; BEV, bevacizumab; CPT-11, irinotecan; KPS, Karnofsky Performance Score; PFS, progression-free survival; OS, overall survival.

Table II. Patient demographics.

	Glioblastoma	Other HGG	All
Number of patients, n (%)	176 (100)	49 (100)	225 (100)
Gender, n (%)			
Male	107 (60.8)	30 (61.2)	137 (60.9)
Female	69 (39.2)	19 (38.8)	88 (39.1)
Age (years)			
Median	55	46	52
Range	19–79	20–70	19–79
Median time from initial diagnosis to start of BEV, days (months)	305 (10.0)	1328 (43.5)	335 (11.0)

HGG, high-grade glioma (anaplastic astrocytoma, oligodendroglioma and mixed glioma); BEV, bevacizumab.

regarding response criteria for anti-angiogenic treatment and 'pseudoresponses', whereby the pseudoresponse reflects a normalisation of abnormally permeable microvessels rather than true tumour shrinkage [13]. In addition, there is a discrepancy between high response rates on conventional radiographic criteria and moderate OS in published phase II trials.

Statistical analysis

Patient characteristics such as gender, age, tumour histology at initial diagnosis and steroid use at the start and during treatment with BEV were assessed. Descriptive statistics using SAS version 8.0 were used to assess: median duration from diagnosis to the date of first BEV treatment administration (days), median duration of BEV therapy (months), KPS before therapy and best score during BEV therapy, and reason for discontinuation of BEV. Time to death after initiation of BEV therapy (days) and time from diagnosis to death (days) were determined using Kaplan–Meier analysis. All analyses are based on a data cut-off point of 31 August 2010.

Results

A total of 225 patients with recurrent HGG were included in this registry [176 patients with glioblastoma and 49 patients with other HGG (anaplastic gliomas of astrocytic, oligodendroglial or mixed phenotypes)]. These diagnoses refer to the histological diagnoses made at first surgery. Patient demographics are shown in Table II. The median age of patients was 52 years (range 19–79). Overall, 20% of patients received BEV monotherapy and 80% were treated with chemotherapy plus BEV. The main combination partner was irinotecan (82% of all combinations), followed by TMZ (9%), lomustine (4.5%) and pegylated liposomal doxorubicin (4.5%). Four of 225 patients received concurrent surgery or irradiation during BEV treatment.

Table III. Changes in KPS and corticosteroid use in patients prior to and during BEV.

	Glioblastoma (n = 176)	Other HGG (n = 49)	All (n = 225)
Steroids at start of treatment, n (%)			
Yes	123 (69.9)	26 (53.1)	149 (66.2)
No	42 (23.9)	15 (30.6)	57 (25.3)
Missing	11 (6.2)	8 (16.3)	19 (8.5)
Steroid interruption during treatment, n (%)			
Yes	48 (27.3)	8 (16.3)	56 (24.9)
No	73 (41.5)	17 (34.7)	90 (40.0)
Not applicable* or missing	55 (31.2)	24 (49.0)	79 (35.1)
KPS prior to treatment, n (%)			
I (80–100)	69 (39.2)	21 (42.9)	90 (40.0)
II (60–70)	63 (35.8)	13 (26.5)	76 (33.8)
III (<60)	30 (17.1)	9 (18.4)	39 (17.3)
Missing	14 (8.0)	6 (12.2)	20 (8.9)
KPS change during treatment, n (%)			
Improved	20 (11.4)	3 (6.1)	23 (10.2)
Stable	120 (68.1)	34 (69.4)	154 (68.4)
Worse	16 (9.1)	4 (8.2)	20 (8.9)
Missing	20 (11.4)	8 (16.3)	28 (12.5)

HGG, high-grade glioma (anaplastic astrocytoma, oligodendroglioma and mixed glioma); KPS, Karnofsky Performance Score, BEV bevacizumab.

*not applicable, where no steroids at start of BEV treatment.

Table IV. Duration of BEV treatment.

	Glioblastoma (n = 176)	Other HGG (n = 49)	All (n = 225)
Duration of BEV treatment (months)			
Median	5.45	6.2	5.5
Range	0.5–39	0.5–36	0.5–39
Patients on treatment, n (%)			
≥6 months	86 (48.9)	25 (51.0)	111 (49.3)
≥1 year	31 (17.6)	12 (24.5)	43 (19.1)
≥2 year	6 (3.4)	4 (8.2)	10 (4.4)

HGG, high-grade glioma (anaplastic astrocytoma, oligodendroglioma and mixed glioma); BEV, bevacizumab.

Overall, 40% of patients had a KPS of ≥80% at the start of BEV treatment; 10% of patients showed improvement in their KPS during treatment (from one group to a better group), whereas 9% showed a decline; no data were available from 13% of patients (Table III). No difference was found between WHO grade III and IV tumours in this respect. During treatment, steroids were stopped in 56 of 149 HGG patients (37.6%) who were receiving steroids at baseline (Table III).

Median duration of BEV-based treatment (with or without additional chemotherapy) was 5.5 months (range 0.5–39; Table IV). Almost half of the patients (49.3%) were treated for more than six months, 19% for more than one year and 10 patients (4.4%) were treated for more than two years.

Overall, median OS from beginning of BEV treatment was 8.5 months, with a median OS of 8.3 months in patients with glioblastoma and 9.1 months in patients with other HGG (Table V). A Kaplan–Meier plot of time-to-death analysis from start of BEV treatment is shown in Figure 1. At the time of this analysis (31 August 2010), 169 patients (75.1%) had died and 56 patients (24.9%) remained alive.

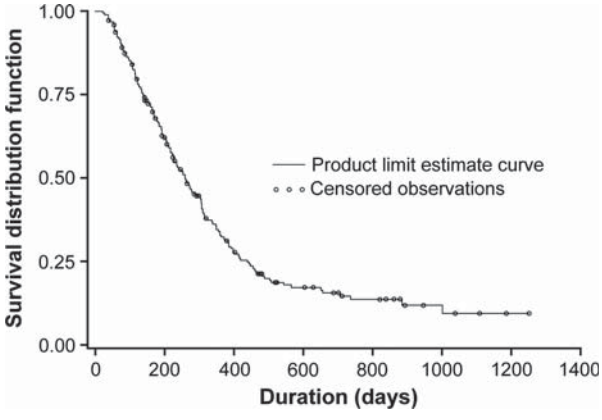

Figure 1. Overall survival from beginning of bevacizumab (BEV) treatment.

There was no clear difference in median duration of BEV-based treatment or median OS from beginning of BEV treatment between the following age groups; <50 years, 51–60 years and >60 years (data not shown).

The main reason for discontinuation of BEV treatment was disease progression. Overall, 76% of patients stopped treatment because of clinical or radiological disease progression or both. A total of 21 patients (9.3%) discontinued treatment due to toxicity (Table VI). Three fatal CNS bleeding complications and two fatalities due to impaired wound healing accounted for toxic deaths in 2.2% of the patient population. Other treatment-related toxicities, such as hypertension and thromboembolic events, were within the range expected based on phase II trials [11].

Discussion

To date, there is no standard of care in recurrent HGG. Recurrences often become symptomatic with increased intracranial pressure and steroids are regularly the treatment of choice to relieve these symptoms [14]. However, steroids are not generally able to maintain their beneficial effect for a long period of time and can also cause disabling side-effects. In contrast to chemotherapeutic agents available for recurrent HGG, the VEGF antibody BEV has the potential to rapidly lower intracranial pressure by modifying vascular permeability. BEV is a well-tolerated drug, causing severe side-effects in only a low percentage of patients.

Our observational registry of an unselected patient cohort with recurrent and pre-treated HGG from 30 different centres aims to reflect community-based experience with BEV. Evidence for the efficacy of BEV-containing treatment regimens for recurrent HGG stems primarily from unicentric or oligocentric phase II trials. Our experience of a larger and less selected population seems of importance and reproduces benefits for patients with recurrent HGG. Within this patient population only a few patients showed a decline in KPS during BEV treatment. Median duration of treatment was 5.5 months and half of all patients were judged to derive benefit from BEV therapy for at least six months and 19% for at least one year. Median OS of over eight months from the start of BEV treatment for all patients confirms the results from phase II trials. In this cohort of recurrent HGG patients, BEV was given as up to and including the last line of therapy. Therefore, it is not likely that OS was confounded by additional therapeutic approaches given after BEV treatment. However, the analysis of such registry data has limitations, including the possibility of a reporting bias of patients in general and underreporting of adverse events.

Table V. Overall survival in HGG patients treated with BEV at recurrence.

	Glioblastoma (n = 176)	Other HGG (n = 49)	All (n = 225)
OS from start of BEV treatment, days			
Median, days (months)	252 (8.3)	277 (9.1)	259 (8.5)
95% CI	216; 305	190; 372	224; 305
OS from diagnosis			
Median, days (months)	668 (21.9)	1972 (64.7)	732 (24.0)
95% CI	569; 762	890; 3485	660; 846

HGG; high-grade glioma (anaplastic astrocytoma, oligodendroglioma and mixed glioma); BEV, bevacizumab; OS, overall survival; CI, confidence interval.

Although an often rapid symptomatic improvement with BEV in recurrent HGG is appealing there are some issues that have not yet been resolved, including mechanisms of action and resistance to BEV in HGG, dosing, optimal drug combination and response assessment [13]. Some of these issues will be addressed in a phase II trial from the EORTC Brain Tumour Group which will explore the sequence of BEV and lomustine in glioblastoma patients at first recurrence. In this four-arm study of 249 patients, OS at 12 months will be the primary endpoint (EORTC 26101; www.eortc.be).

In summary, BEV met with the criteria which are claimed for a palliative treatment for HGG patients, that is the preservation of a stable neurological status, withdrawal of steroids and a good tolerability with an acceptable incidence of side-effects. OS confirms findings from phase II clinical trials [11], suggesting that BEV enriches the limited repertoire of medical treatment options for HGG.

Table VI. Reasons for discontinuation of BEV treatment.

	All (n = 225)
Progression (total PD), n (%)	171 (76.0)
Clinical PD	33 (14.7)
Radiological PD	38 (16.9)
Clinical and radiological PD	100 (44.4)
Toxicity, n (%)	21 (9.3)
Toxicities that led to death (fatal)	5 (2.2)
CNS bleeding (3 fatal, included above)	6 (2.6)
Bleeding other location	2 (0.8)
Wound-healing complications (2 fatal, included above)	5 (2.2)
Thromboembolism (venous or arterial)	4 (1.7)
Hand-foot syndrome‡	1 (0.4)
Proteinuria	2 (0.8)
Diarrhea¥	1 (0.4)
Other reasons, n (%)	24 (10.6)
Not assessed	9 (4.0)
Patient wish	11 (4.8)
Sustained tumor response	4 (1.7)

PD, progressive disease.
*Multiple reasons for BEV discontinuation were possible.
‡Bevacizumab combined with pegylated liposomal doxorubicin.
¥Bevacizumab with irinotecan.

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