Bevacizumab: Is the lower the better for glioblastoma patients in progression?

Lila Sirven-Villaros 1, Véronique Bourg 1, Laurent Suissa 2, Lydiane Mondot 3, Fabien Almairac 4, Denys Fontaine 4, Philippe Paquis 4, Fanny Burel-VandenBos 5, Marc Frenay 1, Pierre Thomas 1, Christine Lebrun-Frenay 1

Keywords
Glioblastoma
Bevacizumab
Recurrence
Progression
Toxicity

Summary

Introduction > Based on the radiological responses obtained with a schedule of ten mg/kg every two weeks bevacizumab was approved by the FDA for recurrent glioblastomas. Due to the negative results concerning overall survival of patients receiving bevacizumab, the European application was rejected. Despite this, many centers apply an off-label prescription. Our aim was to evaluate the safety and efficacy of schedules of low doses of bevacizumab.

Methods > From September 2013 to August 2016, we recruited patients with progressive glioblastoma, whatever the previous treatments. We compared a routine control group (CG) of ten mg/kg, to a low dose group (LDG) composed of 5 subgroups: G5: five mg/kg, G4: four mg/kg, G3: three mg/kg, G2: two mg/kg, G1: one mg/kg, each patient was treated with the same dose every two weeks.

Results > Fifty-three patients were treated: 20 women and 33 men, 24 in the CG and 29 in the LDG. The median age at diagnosis was 62 years [35.0–77.0]. No statistical difference was found in overall survival either for the CG or the LDG (P = 0.086) or among groups (P = 0.251), with even a trend toward improvement for LDG: 62 weeks [20–145] versus 73 weeks [18–178].

progression free survival was comparable: 19.5 weeks [6.0–54.0] for the CG and 15.0 weeks [0.0–134.0] for the LDG (P = 0.221). Bevacizumab was stopped either due to progression (45.1%) or toxicity (52.9%), without significant differences between doses but maybe less toxicities in the LDG (16.7% for toxicity in G1).

Discussion > Use of bevacizumab at progression at lower than usual doses seems to give the same results as the standard dose without giving additional toxicity.

Résumé

Bevacizumab : intérêt de posologies inférieures dans le traitement des glioblastomes à la récidive ?

Introduction > Le bevacizumab a été approuvé par la FDA pour les glioblastomes récidivants sur des réponses radiologiques à dix mg/kg en bimensuel. Malgré le refus d’AMM vu l’absence de preuve d’efficacité sur la survie globale, de nombreux centres européens le prescrivent. Notre objectif était d’évaluer l’efficacité et la tolérance de doses plus basses de bevacizumab pour les glioblastomes récidivants.

Méthodes > Nous avons inclus de septembre 2013 à août 2016 des glioblastomes récidivants quels que soit les traitements antérieurs. À la dose habituelle de dix mg/kg (GC), nous avons comparé des doses plus basses (GB) réparties en cinq sous-groupes : G5 : cinq mg/kg, G4 : quatre mg/kg, G3 : trois mg/kg, G2 : deux mg/kg, G1 : un mg/kg. Chaque patient recevait la même dose toutes les deux semaines.

Résultats > Cinquante-trois patients ont été traités : 20 femmes et 33 hommes, 24 dans GC, 29 dans GB. L’âge médian au diagnostic était de 62 ans [35–77]. La survie globale médiane était comparable entre les groupes, avec même une tendance à l’amélioration dans GB : 62 semaines [20–145] pour GC et 73 semaines [18–178] pour GB, p = 0,086. Aucune différence n’est apparue parmi les sous-groupes (p = 0,251). La survie sans progression était comparable avec une médiane de 19,5 semaines [6,0–54,0] pour GC ; de 15,0 semaines [0,0–134,0] pour GB, p = 0,221. Les causes d’arrêt thérapeutique étaient superposables : 58 % pour toxicité dans GC et 52 % dans GB (avec 17 % dans G1).

Discussion > Utiliser le bevacizumab à des doses plus faibles à la progression de glioblastomes semble entrainer le même effet thérapeutique sans toxicité surajoutée.

Importance of this study

Glioblastomas have poor prognosis and only few schedules have demonstrated efficacy in extending progression free survival or overall survival. Due to its anti-edematous effect, bevacizumab is one of the drugs used at recurrence. It is used with different schedules from five to ten mg/kg every two or three weeks. The present study is an independent exploratory study evaluating the dose-effect. To our knowledge this is the first study to lower the bevacizumab dose from five mg/kg to one mg/kg. We did not find any significant difference throughout the doses either for survival or tolerance. There was a decrease in the known side effects of bevacizumab in the lowest dose group and even a trend toward improvement in overall survival for the lower dose groups. Lowering the dose could help withstanding opposition to this controversial treatment and to obtain a safer result. There is also medico-economical interest in decreasing the dose of bevacizumab, as this molecule is expensive.

Introduction

Glioblastomas (GBM) is the most common primary malignant supra-tentorial brain tumor of adults [1]. Its prognosis is poor, with a mean overall survival (OS) from 15 to 18 months [1] with current treatment settings [2] depending on different factors at diagnosis: age, cognitive or motor impairment, performance status, comorbidities, molecular factors such as the IDH1 or MGMT status [3]. The first-line treatment for GBM consists in cytoreductive surgery followed by radio-chemotherapy with temozolomide (TMZ) 75 mg/m² daily for 42 days followed by six cycles of TMZ 150–200 mg/m² per day, five days per month and per cycle (day one = day 28) [2]. Despite the use of optimal treatments, recurrence is almost unavoidable. Survival over three years is defined as long-term survival and ranges from three to five percent of patients [1] with current treatments [2]. When recurrence or progression occurs, there is no gold standard [4]. Either additional cytoreductive surgery, renewed irradiation,
second-line chemotherapy based on TMZ or nitrosourea, supportive care or inclusion in clinical trials [4] are proposed. Bevacizumab (BEV) is one of the options that can be proposed [5-7]. This drug is a humanized monoclonal antibody that inhibits the vascular endothelial growth factor (VEGF) [8]. Since it binds the ligand of the VEGF receptor, it inhibits the angiogenic cascade [8]. It is already used in association with cytotoxic drugs at a metastatic stage in other cancers such as breast, ovary or colonic cancers [9]. In certain cases, it has been shown to have a cytostatic effect and is consequently used as a long-term continuous treatment [10]. Its toxicity is well known and can be lethal, resulting in an increase in the blood pressure, proteinuria, arterial and venous thrombosis, hemorrhage, digestive perforation or sub-occlusion syndrome, delay in wound healing, optic neuritis, posterior leucoencephalopathy, and toxic death [11], but no information is available concerning modulation of the dose-effect.

Based on conditional approval by the FDA, BEV has been used in neuro-oncology for treatment of GBM patients in the USA since 2009 [12]. Approval was mainly based on the radiological responses but without any consideration of either benefit to OS or expression of the VEGF receptor or the level of VEGF [13,14]. In Europe, in November 2009, the marketing application for BEV to the European Medicines Agency was rejected due to recurrence [15,16] and to adjuvant settings [17,18]. Nevertheless, BEV is still used in an off-label process by many teams outside the USA because physicians are well aware of the BEV effect on peri-tumor edema and on neurological symptoms and therefore on the quality of life [19,20]. However, no information is available about the minimal dose required [21] or the standard schedule to apply. BEV is used from five to ten mg/kg every two or three weeks with no difference in progression free survival (PFS) or OS, but the low dose gives less side effects [5,21].

As there is no documented pharmacodynamic study evaluating the best dose-response, and considering that the choice of current doses in neuro-oncology is empirical [5], we postulated that a lower than usual dose of BEV could be useful in symptomatic care of progressive or recurrent GBM patients initially treated with standard treatment: surgery and radio-chemotherapy followed, when possible, by a nitrosourea-based regimen at the first recurrence [7]. Therefore, we initiated an independent, exploratory and pilot study evaluating multiple dosing schedules of BEV administered to GBM patients in a situation of supportive care or whenever no other treatment could be provided.

**Material and methods**

In our neuro-oncological unit (Côte d’Azur University Hospital, Nice), we prospectively included from September 2013 to August 2016, all progressive or recurrent GBM patients initially treated with surgery followed by radio-chemotherapy, using the usual schedule of radiotherapy with TMZ (75 mg/m²) then TMZ alone (150–200 mg/m²/d each month-six months). At recurrence, depending on various parameters (such as the performance status, comorbidity, tumor location and volume), additional surgery, additional irradiation, second-line chemotherapy based either on TMZ or nitroso urea, was proposed. After these treatments, or when they could not be performed, patients were treated with BEV alone, according to a dose reductive scheme, and included in six successive groups receiving every two weeks either ten mg/kg, the gold standard dose of the control group (CG); five; four; three; two or one mg/kg of BEV respectively, groups G5, G4, G3, G2, or G1. Each patient received the same dose of BEV throughout treatment. The first six patients were included in the CG and then when the total of six patients were enrolled in this group, enrollment into G5 was commenced, and so on, up to G1. The groups from G5 to G1 constituted the LDG. The dose of zero mg/kg, meaning the absence of immunotherapy, therefore corticosteroids alone, was not tested in this study because depending on the neurological symptoms, the patients had various doses of corticosteroids associated with BEV.

To strengthen the statistical power of the study, we added to the CG a cohort of 18 GBM patients treated at the Anti-Cancer Center of Nice who fulfilled the previous inclusion criteria and who were also treated with the standard dose of ten mg/kg.

Exclusion criteria were contraindications concerning BEV use: uncontrolled high blood pressure, any medical history of venous/arterial thrombo-embolism, intra-cerebral hemorrhage or a history of severe gastrointestinal disorders.

For most of our patients, the anatomo-pathological and molecular diagnoses were made before the latest 2016 OMS classification. Therefore, we did not analyze molecular subgroups. All the patients were clinically examined every two weeks before each infusion. Intercurrent events such as epileptic seizures, modification to treatment especially regarding corticosteroids, signs of clinical progression or improvement or side effects of BEV were registered. After BEV was started, a decrease in oral corticotherapy was evaluated whenever it was possible. This was left to the discretion of the investigator.

Patients had a weekly blood test to monitor for hemato-toxicity and every two months, a brain MRI with gadolinium injection looking for a radiological response or progression was performed. The administered dose of BEV was adapted before each infusion taking into account any variation in weight. The status of the performance of the patients had to be sufficient (≤ three) and was checked before each infusion. A favorable performance status (PS) was defined as zero or one and a poor PS as ≥ two.

All information about the treatment and schedule was given to the patients. They also received an information sheet on this drug. Patient’s oral informed consent was collected regarding this treatment and its off-label prescription.
We hypothesized that lowering the dose of BEV for the treatment of glioblastoma patients at recurrence did not worsen their survival.

The primary objective was to compare the OS in the CG and in the LDG. The secondary objective was to compare the safety by looking at the reasons for stopping BEV infusion and to compare survival on BEV. In addition, the survival on BEV and the PFS between the two main groups CG and LDG as well as among the different subgroups of doses (from 1 to 10 mg/kg) were compared. The reasons for stopping BEV infusion were either due to a serious adverse event due to BEV toxicity or to clinico-radiological progression. The PFS was defined as clinical worsening after BEV introduction. Total resection was defined as complete loss of gadolinium enhancement on the post-operative MRI performed within 48-72 h after surgery [22].

As nine patients were still alive at the end of the study on March 7, 2017 and three were still on BEV, we censored the data and survival at this date. Nine months after the end of our study, four patients were still alive and none treated. The univariate and multivariate analyses were adjusted to age, gender, and type of surgery, second-line treatment before BEV and PFS at diagnosis and on the first infusion of BEV. Statistical analyses were conducted using the statistical package STATA SE 10.0. To determine the statistically significant differences between the CG and the LDG, the Chi² test was assessed for categorical variables and the Student’s t test for continuous variables. Continuous variables were represented by the mean and standard deviation. Categorical variables are presented as absolute numbers (%). P < 0.05 was considered significant. The comparison of the survival curves was made using the logRank test.

Results

Demographic characteristics

Fifty-three patients were included, 24 in the CG and 29 in the LDG including 20 women and 33 men (table I). Thirty-five patients were treated at the University Hospital and 18 at the Anti-Cancer Center. We excluded one male patient previously recruited in the LDG subgroup G2 because his GBM was eventually considered to be a neurofibromatosis disease and thus, he may not have been comparable to the other patients.

Patients at diagnosis

The mean age at diagnosis of GBM was 60.8 years old ± 9.3 and the median age at diagnosis was 62.0 years old [35–77]. After surgery, which included total resection in 26.4% (14/53) of the cases, most of the patients were treated with the standard radio-chemotherapy schedule (83.0%, 44/53). The demographic and clinico-radiological characteristics of the population are summarized in (table I). No statistically significant difference was found between the CG and the LDG either for the demographic characteristics or for the clinico-radiological characteristics before BEV infusion except for the proportion of intracranial hypertension symptoms at diagnosis (25.0%, 6/24 in the CG and 0.0%, 0/29 in the LDG) and the PS at diagnosis, which was significantly lower in the CG (50.0%, 12/24 in the CG and 79.3%, 23/29 in the LDG).

Patients at recurrence after the TMZ schedule

Forty-one point five percent (22/53) of the patients received second-line treatment before BEV. 13.2% (7/53) third-line treatment and only one fourth-line treatment. The median number of lines before BEV was 1.0 [1.0–4.0]. The different treatments received before BEV are summarized in (table I). No statistical difference was found when comparing the CG and the LDG.

Evolution with BEV treatment

The PS was favorable (PS < two) before starting BEV infusion in 33.3% (8/24) for the CG and only 20.7% (6/29) for the LDG. The OS was comparable in the CG and the LDG with a mean OS of 72.4 ± 37.2, a median OS of 64.7 weeks [18.3–178.1] and respectively, a mean of 67.0 ± 35.4 weeks and a median of 61.7 weeks [19.9–145.0] for CG and a mean of 77.0 ± 38.6 weeks and a median of 73.0 weeks [18.3–178.1] for the LDG, P = 0.086. Survival on BEV was also comparable in the CG and the LDG with a mean survival on BEV of 37.1 ± 25.8 weeks, a median of 32.6 weeks [1.7–134.0], respectively, a mean of 34.9 ± 20.2 weeks, a median of 33.3 weeks [2.2–71.9] for the CG and a mean of 38.8 ± 29.9 weeks and a median of 32.6 weeks [1.7–134.0] for the LDG, P = 0.249. We did not find any statistical difference between the CG and LDG when comparing PFS, with a mean PFS of 24.4 ± 26.1 weeks and a median PFS of 17.0 weeks [0.0–134.0], P = 0.221. For the CG, the mean PFS was 23.3 weeks ± 12.5 and the median PFS was 19.5 weeks [6.0–54.0]. For the LDG, the mean PFS was 24.8 weeks ± 30.0 and the median PFS was 15.0 weeks [0.0–134.0]. To date, there is one long survivor who is still alive in the LDG (G5) and the mean OS of eight patients was over two years (four in the CG and four in the LDG with one in G4, two in G2 and one in G1). The results concerning evolution on BEV are summarized in (table II). The OS curves are shown in (figure 1) and survival curves on BEV in (figure 2). The time between diagnosis and the first BEV infusion (mean of 38.0 weeks), the duration of BEV treatment (mean of 27.3 weeks) and the time between the last BEV infusion and death (mean of 10.3 weeks) were comparable in the two groups. The age at diagnosis was the only statistically significant parameter of adjustment in the multivariate analysis (P = 0.021) of the duration of BEV treatment with an OR of 0.9 [0.82–0.98], meaning that each year deducted from the age of a patient at diagnosis increases the chance by 11% of being treated with BEV for more than six months. The age at diagnosis of GBM was independently associated with the duration of BEV treatment. In contrast, the gender, the type of initial surgery, the presence or not of intermediary treatment between radio-chemotherapy and BEV, the PS at the first occurrence of progression and at the beginning of BEV were not associated.
To cite this article: Sirven-Villaros I, et al. Bevacizumab: Is the lower the better for glioblastoma patients in progression? Bull Cancer (2018), [https://doi.org/10.1016/j.bulcan.2018.07.010](https://doi.org/10.1016/j.bulcan.2018.07.010)

**Table I**

Demographic characteristics before BEV

<table>
<thead>
<tr>
<th>Groups</th>
<th>CG</th>
<th>LDG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>24</td>
<td>29</td>
<td></td>
</tr>
<tr>
<td>Gender male</td>
<td>14/24 (58.3%)</td>
<td>19/29 (65.5%)</td>
<td>0.776</td>
</tr>
<tr>
<td>Mean age at diagnosis (years)</td>
<td>61.7 ± 9.2</td>
<td>60.1 ± 9.5</td>
<td>0.536</td>
</tr>
<tr>
<td>Comorbidities and medical history</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4/24 (16.7%)</td>
<td>12/29 (41.4%)</td>
<td>0.729</td>
</tr>
<tr>
<td>Abdominal surgery</td>
<td>3/24 (12.5%)</td>
<td>11/29 (37.9%)</td>
<td>0.059</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2/24 (8.3%)</td>
<td>3/29 (10.4%)</td>
<td>0.803</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0/24 (0.0%)</td>
<td>3/29 (10.4%)</td>
<td>0.242</td>
</tr>
<tr>
<td>Coronaropathy</td>
<td>1/24 (4.2%)</td>
<td>2/29 (6.9%)</td>
<td>0.669</td>
</tr>
<tr>
<td>Nervous breakdown</td>
<td>0/24 (0.0%)</td>
<td>2/29 (6.9%)</td>
<td>0.495</td>
</tr>
<tr>
<td>Thyroid disease</td>
<td>1/24 (4.2%)</td>
<td>2/29 (6.9%)</td>
<td>0.669</td>
</tr>
<tr>
<td>Chronic kidney failure</td>
<td>1/24 (4.2%)</td>
<td>0/29 (0.0%)</td>
<td>0.453</td>
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<tr>
<td>Initial symptoms</td>
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</tr>
<tr>
<td>Focal deficit</td>
<td>10/24 (41.7%)</td>
<td>15/29 (51.7%)</td>
<td>0.583</td>
</tr>
<tr>
<td>Epileptic seizure</td>
<td>6/24 (25.0%)</td>
<td>11/29 (37.9%)</td>
<td>0.384</td>
</tr>
<tr>
<td>Intracranial hypertension</td>
<td>6/24 (25.0%)</td>
<td>0/29 (0.0%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Cognitive impairment</td>
<td>2/24 (8.3%)</td>
<td>3/29 (10.4%)</td>
<td>0.803</td>
</tr>
<tr>
<td>General State before BEV</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PS &lt; two at diagnosis</td>
<td>12/24 (50.0%)</td>
<td>25/29 (86.2%)</td>
<td>0.007</td>
</tr>
<tr>
<td>PS &lt; two at the first progression</td>
<td>12/24 (50.0%)</td>
<td>9/29 (31.0%)</td>
<td>0.259</td>
</tr>
<tr>
<td>PS &lt; two at the beginning of BEV</td>
<td>8/24 (33.3%)</td>
<td>6/29 (20.7%)</td>
<td>0.358</td>
</tr>
<tr>
<td>Initial surgery</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biopsy</td>
<td>6/24 (25.0%)</td>
<td>14/29 (48.3%)</td>
<td>0.082</td>
</tr>
<tr>
<td>Partial resection</td>
<td>9/24 (37.5%)</td>
<td>10/29 (34.5%)</td>
<td>0.820</td>
</tr>
<tr>
<td>Total resection</td>
<td>9/24 (37.5%)</td>
<td>5/29 (17.2%)</td>
<td>0.096</td>
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<tr>
<td>Outcome before BEV</td>
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<td></td>
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<tr>
<td>Standard RT-TMZ schedule</td>
<td>22/24 (91.7%)</td>
<td>22/29 (75.9%)</td>
<td>0.127</td>
</tr>
<tr>
<td>Complete RT-TMZ schedule</td>
<td>10/24 (41.7%)</td>
<td>4/29 (13.8%)</td>
<td>0.022</td>
</tr>
<tr>
<td>Fotemustine-Gisplatin-VP16(^1)</td>
<td>0/24 (0.0%)</td>
<td>4/29 (13.8%)</td>
<td>0.058</td>
</tr>
<tr>
<td>PCV followed by RT(^2)</td>
<td>1/24 (4.2%)</td>
<td>1/29 (3.4%)</td>
<td>0.891</td>
</tr>
<tr>
<td>TMZ alone(^3)</td>
<td>0/24 (0.0%)</td>
<td>1/29 (3.4%)</td>
<td>0.358</td>
</tr>
<tr>
<td>Nitrosourea</td>
<td>12/24 (50.0%)</td>
<td>8/29 (27.6%)</td>
<td>0.094</td>
</tr>
<tr>
<td>Crizotinib</td>
<td>0/24 (0.0%)</td>
<td>2/29 (6.9%)</td>
<td>0.495</td>
</tr>
<tr>
<td>Second irradiation</td>
<td>0/24 (0.0%)</td>
<td>1/29 (3.4%)</td>
<td>0.358</td>
</tr>
<tr>
<td>Second surgery</td>
<td>4/24 (16.7%)</td>
<td>6/29 (20.7%)</td>
<td>0.709</td>
</tr>
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</table>
In the linear regression analysis, only a favorable PS before BEV improved survival with BEV, but without statistical significance ($P = 0.0528$). The previous variables did not affect survival with BEV.

We analyzed the MRI performed every 2 months for each patient and found that the effect of BEV on capillary permeability could also be found even for the lowest dose of BEV with an anti-edematous effect on T2 FLAIR sequences and a decrease in the gadolinium enhancement on the injected T1 sequences, as shown in the supplementary figure.

**Toxicity**

BEV infusion had to be stopped either in the case of progression (43.4%: 23/53) or toxicity (50.9%: 27/53), respectively for progression: 41.7% (10/24) in the CG and 48.3% (13/29) in the LDG and respectively for toxicity: 54.2% (13/24) in the CG and 48.3% (14/29) in the LDG. One patient (1.9%) in the CG and two patients (3.8%) in the LDG were still treated at the end of the study. Of the 28 reported cases of toxicity, 25 were serious adverse events of grade four on the WHO toxicity grading scale. No deaths due to toxicity were reported. The reasons for

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**Table I (Continued)**

<table>
<thead>
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<th>Groups</th>
<th>CG</th>
<th>LDG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Third surgery</td>
<td>0/24 (0.0%)</td>
<td>1/29 (3.4%)</td>
<td>0.358</td>
</tr>
<tr>
<td>Second-line before BEV</td>
<td>12/24 (50.0%)</td>
<td>10/29 (34.4%)</td>
<td>0.254</td>
</tr>
<tr>
<td>Third-line before BEV</td>
<td>2/24 (8.4%)</td>
<td>5/29 (17.2%)</td>
<td>0.340</td>
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<tr>
<td>Fourth-line before BEV</td>
<td>0/24 (0.0%)</td>
<td>1/29 (3.4%)</td>
<td>0.358</td>
</tr>
<tr>
<td>Median number of lines before BEV</td>
<td>2 [1-3]</td>
<td>1 [1-4]</td>
<td></td>
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</table>


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**Table II**

<table>
<thead>
<tr>
<th>(Weeks)</th>
<th>Total</th>
<th>CG</th>
<th>LDG</th>
<th>P</th>
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<tbody>
<tr>
<td>Number of patients</td>
<td>53</td>
<td>24</td>
<td>29</td>
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</tr>
<tr>
<td>Mean time from diagnosis to BEV</td>
<td>38.0 ± 28.1</td>
<td>34.3 ± 28.1</td>
<td>41.2 ± 28.2</td>
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<tr>
<td>Median time from diagnosis to BEV</td>
<td>23.3 [6.6-112.4]</td>
<td>22.0 [9.0-112.4]</td>
<td>33.7 [6.6-106.9]</td>
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<tr>
<td>Mean duration of BEV treatment</td>
<td>26.8 ± 23.1</td>
<td>29.3 ± 17.5</td>
<td>24.7 ± 27.0</td>
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<tr>
<td>Median duration of BEV treatment</td>
<td>22.1 [0.1-134.0]</td>
<td>27.5 [1.7-67.5]</td>
<td>19.4 [0.1-134.0]</td>
<td></td>
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<tr>
<td>Mean OS</td>
<td>72.4 ± 37.2</td>
<td>67.0 ± 35.4</td>
<td>77.0 ± 38.6</td>
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<tr>
<td>Median OS</td>
<td>64.7 [18.3-178.1]</td>
<td>61.7 [19.9-145.0]</td>
<td>73.0 [18.3-178.1]</td>
<td>0.086</td>
</tr>
<tr>
<td>Mean PFS</td>
<td>24.4 ± 26.1</td>
<td>23.3 ± 12.5</td>
<td>24.8 ± 30.2</td>
<td></td>
</tr>
<tr>
<td>Median PFS</td>
<td>17.0 [0.0-134.0]</td>
<td>19.5 [6.0-54.0]</td>
<td>15.0 [0.0-143.0]</td>
<td>0.221</td>
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<tr>
<td>Number of patients with a mean OS &gt; three years</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Number of patients with a mean OS &gt; two years</td>
<td>8</td>
<td>4</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Mean survival on BEV</td>
<td>37.1 ± 25.9</td>
<td>34.9 ± 20.2</td>
<td>32.6 ± 29.9</td>
<td></td>
</tr>
<tr>
<td>Median survival on BEV</td>
<td>32.6 [1.7-134.0]</td>
<td>33.3 [2.2-71.9]</td>
<td>32.6 [1.7-134.0]</td>
<td>0.249</td>
</tr>
<tr>
<td>Mean time between last BEV and death</td>
<td>10.4 ± 13.0</td>
<td>5.9 ± 6.6</td>
<td>14.1 ± 15.8</td>
<td></td>
</tr>
<tr>
<td>Median time between last BEV and death</td>
<td>5.3 [0.0-65.5]</td>
<td>4.1 [0.5-32.6]</td>
<td>7.6 [0.0-65.5]</td>
<td></td>
</tr>
</tbody>
</table>

CG: control group; LDG: low doses group; OS: overall survival; BEV: bevacizumab; PFS: progression free survival after BEV introduction.
FIGURE 1
Overall survival curves
CG: control group; LDG: low dose group. * no statistical difference was found. $P = 0.086$.

stopping BEV infusion are summarized in (figure 3A, B). No correlation between the cumulative dose of BEV and the appearance of toxicity was found, as shown in (figure 3C).

Subgroup analysis
No significant difference was found when comparing, on one hand, the CG and G5, and on the other hand G4, G3, G2 and G1 either for the mean OS ($P = 0.223$) or for survival on BEV ($P = 0.615$). When we compared each group separately, there was no difference either for the mean OS ($P = 0.2501$) or for survival on BEV ($P = 0.249$). The survival curves of all the subgroups for the mean OS and the survival on BEV are presented in (figure 4A, B).

Analysis of the toxicity suggested that the lower doses of BEV were better since the percentage of patients who stopped BEV because of toxicity were respectively, for G5: 80.0% (4/5), G4: 83.3% (5/6), G3: 40.0% (2/5), G2: 40.0% (2/5), G1: 16.7% (1/6), as shown in (figure 4C).

Discussion
Compared to the literature, the demographic data, the mean OS, the mean survival of patients on BEV and the PFS were comparable to those reported in the present study [8] supplementary table, whatever the group, the CG or LDG, meaning that treating patients with a lower dose of BEV was as efficient as the standard schedule. We did not find any difference throughout the doses, from ten to one mg/kg. However, the results are based on groups of small populations.

The PS at diagnosis was significantly more often favorable in the LDG (50.0% for the CG versus 86.2% for the LDG) but this difference was reversed before beginning BEV (33.3% for the CG versus 20.7% for the LDG). This result shows that the population was non-selected regarding the general status, with a rather poor PS before BEV, and also regarding the number of treatment lines before BEV. This could have been a harbinger of poorer survival but the survival of our patients was comparable to that reported in the literature, even though some of the data is distorted due to censure. In most of the studies that have analyzed BEV, the patients included had to have a favorable general status (usually Karnofsky > 60 or 70/100 or PS ≤ two) [23] and BEV was generally used at first recurrence [14]. The response to BEV varied depending on the patient and cannot be predicted. To date, there are no tools available to evaluate response [24,25]. Depending on the patient, the response is variable in time and efficacy, and the only prognostic factor we identified was PS before BEV. In fact, in a multivariate analysis, we found that a favorable PS before beginning BEV improved slightly survival on BEV, but with no statistical significance ($P = 0.052$). However, the results in the literature somewhat diverge [13,16,25-29]. We also found that a younger age at
diagnosis significantly improved the duration of BEV treatment with an OR of 0.9 [0.82–0.98], but it is unknown if this means that BEV is more efficient in younger patients. No difference was found for toxicity, meaning that treating with lower doses is as safe as with the gold standard dose. There was even a slight decrease in toxicity in the LDG, which could explain the trend to improvement in the mean OS in the LDG: only 16.7% of patients stopped BEV due to toxicity in G1. The same was found by Lorigs et al. [30] who reported an improvement in PFS and OS proportionally inverted to the dose ($r = -0.48, P > 0.00001$). This study [30] and the study of Blumenthal et al. [31] also found a decrease in toxicity for five mg/kg versus ten mg/kg. This was also the case for results of a dose review of the use of BEV in oncology, especially for ovary and colonic cancer [9].

The first study to describe the use of BEV for treatment of patients presenting with GBM was presented in 2005 by Stark Vance at the dose of five mg/kg BEV every two weeks. In subsequent studies, without any justification or further investigation, the recommended dose was doubled [5]. Approval by the FDA was given in May 2009 for recurrent GBM patients, as second-line monotherapy at the dose of ten mg/kg every two weeks [12], based mainly on the radiological responses and for 25% of partial responses for a mean duration of four months, which was obtained in a single arm phase II trial of BEV with irinotecan added at progression and a phase II trial with a combination of BEV and irinotecan at different doses and timing [13,14]. In a study by Piccioni et al. [32], the PFS reached four months after the first infusion of BEV, which was initiated at different times of recurrence.

Even though the European Medicines Agency rejected the application for the use of BEV because of the lack of proof of benefit for survival, a lot of European teams apply an off-label prescription at recurrence, associated with or without a cytotoxic drug. Studies have shown that BEV should be used as monotherapy: several drug-associated clinical trials did not find any benefit and in some cases association was harmful [17], as with cetuximab [17]. To date, there is no evidence, either at recurrence [8,14,19,24,33–36] or in adjuvant settings [8,17,18], showing benefit to OS in association with BEV in glioblastomas but an increase in PFS [17,18]. The phase III study of Wick et al. found a PFS of 4.2 months with the combination versus 1.5 months with monotherapy but also found more frequently serious adverse events (grade 3 to 5 adverse events) with the combination (63.6%) than with lomustine alone (38.1%) [35]. In adjuvant settings trials, the PFS was also increased in the RTOG 0825 phase II study and the AVAglio study, which found respectively, 10.7 months versus 7.3 months for RTOG 0825 and 10.6 months versus 6.2 months for AVAglio [17,18]. Both studies also found more side effects in the adjuvant setting using BEV. In the BELOB study [37], the use of BEV alone or in

**Figure 2**

*Survival curves on BEV*

CG: control group; LDG: low dose group; * no statistical difference was found. $P = 0.249$. 

To cite this article: Sirven-Villaros L, et al. Bevacizumab: Is the lower the better for glioblastoma patients in progression? Bull Cancer (2018), https://doi.org/10.1016/j.bullcan.2018.07.010
combination with lomustine did not improve the quality of life of the patients. The use of BEV is therefore controversial. Several announcements concerning delisting of BEV in France have been made, despite the possibility of improving PFS and of clinical benefit due to temporary resorption of edema [20]. Nevertheless, the clinical side effects of BEV, which can be very serious adverse events that affect the quality of life, need to be integrated into the benefit-risk ratio. In current practice, BEV is usually used as a last line of treatment after failure of all other treatments. At progression on BEV, depending on the neurological and general state of the patient, some neuro-oncologists consider that BEV should be continued due to its benefit to OS and PFS [10].

**Internal validity, bias and limits**

As a result of the potential bias of our study, due to the number of patients per groups, we cannot provide a conclusion that is statistical relevant but can provide a rational opinion concerning

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**Figure 3**

Reasons for stopping BEV infusion

A. Due to toxicities.
B. Due to progression.
C. Occurrence of adverse events on BEV.

CG: control group; LDG: low dose group; BEV: bevacizumab.

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**Table 1**

(Treatment with BEV) | CG | LDG
---|---|---
Dosage | 0.1 mg/kg | 0.5 mg/kg | 1 mg/kg | 2 mg/kg | 3 mg/kg | 5 mg/kg
Pulmonary embolism | 8.3 and 11.3 | 5.8 and 8.6 | 3.6 and 5.4 | 2.9 | 2.1 | 1.7
Deep vein thrombosis | 36.1 | 32.0 | 28.6 | 21.0 | 18.2 | 13.5
Ischemic stroke | 32.0 and 31.6 | 28.6 | 25.0 | 21.0 | 18.2 | 13.5
Silent ischemic lesion | 45.7 | 45.7 | 45.7 | 45.7 | 45.7 | 45.7
Intra cerebral hemorrhage | 36.1 | 32.0 | 28.6 | 21.0 | 18.2 | 13.5
Intra ocular hemorrhage | 18.1 | 18.1 | 18.1 | 18.1 | 18.1 | 18.1
Digestive occlusion / perforation | 9.0 and 11.3 | 5.1 and 5.1 | 3.4 and 3.4 | 2.9 | 2.1 | 1.7
Thrombotic Thrombocytopenic Purpura | 42.4 | 42.4 | 42.4 | 42.4 | 42.4 | 42.4
Posterior reversible encephalopathy syndrome | 42.4 | 42.4 | 42.4 | 42.4 | 42.4 | 42.4
Bilateral retrobulbar optic neuritis | 9.0 and 10.9 | 42.8 | 31.8 | 21.0 | 18.2 | 13.5

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the subgroup analysis. At the end of the study, the survival data were distorted because nine patients were still alive and three were still on treatment. So, we artificially ended their survival by censoring the data. We did not add to this real-life report, any quality of life scale that would have been interesting in this palliative context.

Among the serious adverse events that occurred in our population, not all were attributable to BEV. Several patients had cardiovascular risk factors and some could not be weaned off corticosteroids. Moreover, in the cases of ischemic stroke or pulmonary embolism, a perturbation to coagulation, which is inherent to the state of cancer, should not be forgotten.

**Strengths of our study**

This cohort is, to our knowledge, the first to study treatment of GBM patients with doses lower than five mg/kg. We included a sufficient number of patients to obtain statistically robust data to compare the CG and LDG. There is also medico-economical interest in reducing the doses since it also reduces the costs, which is even more interesting as BEV is an expensive and controversial molecule used in palliative settings.

A cost effectiveness analysis reported that each year of life gained for each patient treated with a combination of BEV and irinotecan costed 46,401.99€ [38]. Another cost effectiveness study found that the ratio to obtain six month PFS at progression was of 4,112.97€/year for fotemustine, 5,470.05€/year for extended TMZ and 15,122.49€/year for BEV [39], which could be brought to 1,512.25€/year for the lowest dose of BEV that we tested and therefore would be more competitive.

**Conclusion**

To our knowledge this study is the first to evaluate the effect of lowering the dose of BEV. We did not find any difference in survival or tolerance for the different doses of BEV. The strategy of decreasing the dose to enhance supportive care can be an interesting way to reduce its adverse events while increasing its medico-economical interest. Further studies are required, especially concerning the use of lower doses in the daily clinical practice, and the impact on the quality of life compared to corticosteroids.

**Funding:** none.

**Disclosure of interest:** the authors declare that they have no competing interest.

**Supplementary data**

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.bulcan.2018.07.010.
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