Second-Line Chemotherapy in Recurrent Glioblastoma: A 2-Cohort Study

Bruno F. Carvalho\textsuperscript{a}  Ana C. Fernandes\textsuperscript{b}  Daniela S. Almeida\textsuperscript{b}  Luisa V. Sampaio\textsuperscript{c}  Andreia Costa\textsuperscript{b}  Claudia Caeiro\textsuperscript{b}  Ligia Osório\textsuperscript{d}  Ligia Castro\textsuperscript{e}  Paulo Linhares\textsuperscript{a}  Margarida Damasceno\textsuperscript{b}  Rui C. Vaz\textsuperscript{a,f}

\textsuperscript{a} Department of Neurosurgery, Centro Hospitalar de São João, Porto, Portugal;  
\textsuperscript{b} Department of Medical Oncology, Centro Hospitalar de São João, Porto, Portugal;  
\textsuperscript{c} Department of Neuroradiology, Centro Hospitalar de São João, Porto, Portugal;  
\textsuperscript{d} Department of Radiotherapy, Centro Hospitalar de São João, Porto, Portugal;  
\textsuperscript{e} Department of Pathology, Centro Hospitalar de São João, Porto, Portugal;  
\textsuperscript{f} Neurosciences Department, Hospital CUF Porto, Portugal

Introduction

Glioblastoma (GB) is the most common malignant primary central nervous system (CNS) tumor in adults. The standard of care consists of multimodal therapy including surgical resection, radiotherapy and temozolomide (TMZ), but nearly all patients experience disease progression.

The prognosis of recurrent GB remains dismal, with an estimated 5-year survival rate of only 3.4\% \cite{1}. No standard treatment has been established, but the currently available therapies in selected patients include second surgery, re-irradiation, salvage chemotherapy, and biologic agents \cite{2}. Most patients are offered salvage chemotherapeutic or biological agents, attaining low response rates (RRs) and minimal benefit in progression-free survival (PFS) and overall survival (OS) rates. Typical RRs range from 5 to 20\%, the typical 6-month PFS ranges from 10 to 24\%, and the median OS from 5 to 7.5 months \cite{3–6}.

These tumors have been associated with extensive tumor necrosis, intense vascular proliferation and increased expression of angiogenic factors, the most important of which is the vascular endothelial growth factor (VEGF). VEGF is a major regulator of angiogenesis and its overexpression is associated with poor prognosis \cite{7, 8}.

The introduction of anti-angiogenic therapy, namely bevacizumab, a humanized monoclonal immunoglobulin (Ig) G1 antibody that binds to and inhibits the biological activity of human VEGF-A, resulted in improved RRs and extended PFS. Vredenburgh et al. \cite{9} supported these conclusions in their landmark study with a reported RR of 57\% and a PFS at 6 months of 46\%.

The phase II BRAIN trial (multicenter, open-label, noncomparative Genentech\textsuperscript{®} sponsored trial) achieved an RR of 38\% with a 6-month PFS of 50.3\% (bevacizumab + irinotecan group) and an

Keywords

Bevacizumab · Recurrent glioblastoma

Summary

Background: Glioblastoma (GB) is the most common malignant primary central nervous system tumor in adults. Standard-of-care therapy includes surgical resection, radiotherapy and temozolomide, but nearly all patients experience disease progression. The purpose of this study was to describe 2 cohorts of patients with recurrent GB submitted to second-line treatment with procarbazine/lomustine/vincristine (PCV) or bevacizumab/irinotecan (BI).

Material and Methods: Retrospective analysis of GB patients treated in our center with PCV or BI, after progression with temozolomide, between 2004 and 2012. Results: Among 60 patients, 41 were treated with BI and 19 with PCV. According to the Macdonald criteria, the overall response rate in the BI group was 66\% (n = 27) while it was 11\% (n = 2) in the PCV group. The median progression-free survival was 5 and 3 months in the BI and PCV group, respectively. The median overall survival (OS) since second-line chemotherapy was 9 months in the BI group and 5 months in the PCV group. The latter group had a worse toxicity profile (grade 3–4: 52.6\% vs. 22.0\%; grade 1–2: 89.5\% vs. 68.3\%).

Conclusions: The BI cohort had higher response rates, almost twice the OS and a lower degree of toxicity in contrast to the PCV group. The small number of patients and historical cohorts limits these comparisons.

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objective RR of 28% and a PFS at 6 months of 42.6% (bevacizumab alone group), which is significantly superior to the historical controls [10].

Some of the controversy around bevacizumab derives from its main mechanism of action, i.e. the ability to neutralize the VEGF which results in the stabilization of the blood-brain barrier, which in turn can prevent radiographic enhancement and thus mask tumor growth [11].

Although anti-angiogenic therapies have showed significant improvement in recurrent GB patients, predicting who benefits the most and establishing optimal schedules and combination therapies, in addition to the validation of biochemical and radiological biomarkers of tumor response, remain evolving areas of research.

The purpose of this study was to retrospectively describe 2 cohorts of recurrent GB submitted to second-line treatment with procarbazine/lomustine/vincristine (PCV) and bevacizumab/irinotecan (BI), focusing on efficacy and the safety profile.

Material and Methods

Patient Selection

We performed a retrospective analysis of the records of all patients with histologically confirmed progressive GB under TMZ between 2004 and 2012 treated at our institution.

All patients had been initially treated according to standard first-line treatment with TMZ, administered at a dose of 75 mg/m² concurrent with daily external-beam radiation therapy (RT) (2 Gy/fraction, for a total of 60 Gy in 30 fractions) and followed by adjuvant TMZ at 150–200 mg/m² for 5 days every 28 days until progression.

We analyzed all patients treated with second-line bevacizumab (10 mg/kg) + irinotecan (340 or 125 mg/m², with or without concomitant enzyme-inducing anti-epileptic drugs, respectively) every 2 weeks or PCV (procarbazine 100 mg/m² per os (p.o.), 10 days (days 2–11), lomustine 100 mg/m² p.o. at day 1, vincristine 2 mg intravenously (i.v.) at day 1) every 6 weeks.

All patients with GB recurrence and without chemotherapy contraindications were proposed to second-line chemotherapy, with or without second surgery (if indicated). Chemotherapy contraindications were defined as: Eastern Cooperative Oncology Group (ECOG) performance status > 2, clinically significant cardiovascular disease, and previous arterial thromboembolism event.

Patient Demographics and Characteristics

In this study, 60 patients were included, of which 41 were treated with BI and 19 with PCV. The majority were male (68.3%, n = 41), with a median age of 56.5 years (range 34–73 years).

At first presentation, most patients (66.7%, n = 40) had undergone a complete macroscopic resection at the time of diagnosis. Post-surgery, the patients received standard first-line treatment with concomitant RT and TMZ followed by adjuvant TMZ (median number of 6 cycles, range 1–28 cycles). The median time from adjuvant TMZ conclusion to second-line chemotherapy was 1 month in both groups (BI: 0–12 months; PCV: 0–10 months).

The type of first progression was focal in 86.7% (n = 52) and multifocal in the remaining patients. A second surgery was performed in 20.0% (n = 12), with a complete macroscopic resection in 10 (83.3%) of these 12 patients.

All patients included had an ECOG performance status of ≤ 2 at the beginning of second-line chemotherapy, 79.0% (n = 49) were under corticosteroids, and 53.2% (n = 33) were medicated with anti-epileptic drugs.

The patient characteristics in the BI and PCV groups are described in table 1. The time to first progression was identical between the groups (BI 9.0 months, 95% confidence interval (CI) 7.2–10.8 months vs. PCV 9.0 months, 95% CI 6.9–11.1 months; p = 0.121). A comparative analysis of the baseline characteristics between the 2 groups showed no difference regarding age (p = 0.880, t-test), ECOG performance status (p = 0.070, Mann-Whitney U test), type of resection (p = 0.653, Fisher’s exact test), or second surgery (p = 0.49, Fisher’s exact test). Multifocal disease was present in only 3 patients, all of them in the BI group.

Results

Objective Response Assessment

The median number of cycles of BI and PCV was 9.0 (range 1–40) and 2.0 (range 1–5), respectively. The response assessment

Patterns of progression were classified as focal, multifocal, or diffuse non-enhancing according to T1 gadolinium and T2/FLAIR imaging responses.

OS and PFS were calculated from the first day of second-line treatment. Primary endpoints were OR and median PFS. Secondary endpoints were median OS, the safety profile, and the evaluation of prognostic factors.

Statistical Analysis

Survival distributions were estimated using the Kaplan-Meier method. Variability between criteria classification (Macdonald and RANO) was determined by kappa statistic. Statistical tests were 2-sided and significance was set at p < 0.05. Analyses were performed using SPSS v20.0.

References


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Objective Response Assessment

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in these 2 groups was evaluated according to the Macdonald and RANO criteria.

**Macdonald Criteria**

It was possible to assess the response in only 58 patients, since in 2 patients (both in the PCV group) the treatment was discontinued before radiologic evaluation due to toxicity (thrombocytopenia and sepsis). The majority of patients in the BI group experienced clinical improvement or stabilization (78.0%, n = 32), while in the PCV group the majority had clinical deterioration under treatment (78.9%, n = 15). Most patients were under corticotherapy at the beginning of second-line treatment (85.0%, n = 51): 82.9% (n = 34) in the BI group and 89.5% (n = 17) in the PCV group. Dose reduction was possible in 8 patients (19.5%) and discontinued in 1 patient under BI. Only 1 patient in the BI group had an increase in the dose of corticosteroids. On the other hand, in the PCV group, no patients reduced or suspended the corticotherapy and in the majority of cases the dose was increased (57.9%, n = 11). In the BI

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Total (n = 60)</th>
<th>BI (n = 41)</th>
<th>PCV (n = 19)</th>
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</thead>
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<tr>
<td>Age, years</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>57.0</td>
<td>56.0</td>
</tr>
<tr>
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<td>34–72</td>
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<tr>
<td>Gender</td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>68.3% (n = 41)</td>
<td>68.3% (n = 28)</td>
<td>68.4% (n = 13)</td>
</tr>
<tr>
<td>Female</td>
<td>31.7% (n = 19)</td>
<td>31.7% (n = 13)</td>
<td>31.6% (n = 6)</td>
</tr>
<tr>
<td>Initial surgery</td>
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</tr>
<tr>
<td>Complete macroscopic resection</td>
<td>66.7% (n = 40)</td>
<td>65.9% (n = 27)</td>
<td>68.4% (n = 13)</td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>25.0% (n = 15)</td>
<td>24.4% (n = 10)</td>
<td>26.3% (n = 5)</td>
</tr>
<tr>
<td>Stereotactic biopsy</td>
<td>8.3% (n = 5)</td>
<td>9.8% (n = 4)</td>
<td>5.3% (n = 1)</td>
</tr>
<tr>
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<td></td>
<td></td>
</tr>
<tr>
<td>Unifocal</td>
<td>95.0% (n = 57)</td>
<td>92.7% (n = 38)</td>
<td>100.0% (n = 19)</td>
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<tr>
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<td>5.0% (n = 3)</td>
<td>7.3% (n = 3)</td>
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<td>Localization</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Left</td>
<td>70.0% (n = 42)</td>
<td>68.3% (n = 28)</td>
<td>73.7% (n = 14)</td>
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<tr>
<td>Right</td>
<td>21.7% (n = 13)</td>
<td>19.5% (n = 8)</td>
<td>26.3% (n = 5)</td>
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<td>Bilateral</td>
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<td>12.2% (n = 5)</td>
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<td>Number of lobes</td>
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</tr>
<tr>
<td>1</td>
<td>60.0% (n = 36)</td>
<td>56.1% (n = 23)</td>
<td>68.4% (n = 13)</td>
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<td>≥ 2</td>
<td>40.0% (n = 24)</td>
<td>43.9% (n = 18)</td>
<td>31.6% (n = 6)</td>
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<td>Median tumor size, cm</td>
<td>3.79</td>
<td>4.17</td>
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<td>Number of cycles of TMZ</td>
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<td>6.0</td>
<td>6.0</td>
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<tr>
<td>Range</td>
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<td>1–28</td>
<td>1–10</td>
</tr>
<tr>
<td>Type of first progression</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Focal</td>
<td>86.7% (n = 52)</td>
<td>90.2% (n = 37)</td>
<td>78.9% (n = 15)</td>
</tr>
<tr>
<td>Multifocal</td>
<td>13.3% (n = 8)</td>
<td>9.8% (n = 4)</td>
<td>21.1% (n = 4)</td>
</tr>
<tr>
<td>Surgery</td>
<td>20.0% (n = 12)</td>
<td>17.1% (n = 7)</td>
<td>26.3% (n = 5)</td>
</tr>
<tr>
<td>Complete macroscopic resection</td>
<td>83.3% (n = 10)</td>
<td>85.7% (n = 6)</td>
<td>80.0% (n = 4)</td>
</tr>
<tr>
<td>Subtotal resection</td>
<td>16.7% (n = 2)</td>
<td>14.3% (n = 1)</td>
<td>20.0% (n = 1)</td>
</tr>
<tr>
<td>ECOG at 2nd-line CT</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>0</td>
<td>21.7% (n = 13)</td>
<td>24.4% (n = 10)</td>
<td>15.8% (n = 3)</td>
</tr>
<tr>
<td>1</td>
<td>66.7% (n = 40)</td>
<td>70.7% (n = 29)</td>
<td>57.9% (n = 11)</td>
</tr>
<tr>
<td>2</td>
<td>11.7% (n = 7)</td>
<td>4.9% (n = 2)</td>
<td>26.3% (n = 5)</td>
</tr>
<tr>
<td>Median time from completion of RT to beginning of 2nd-line CT, months</td>
<td>7.5 (3.5–54)</td>
<td>8 (3.5–15)</td>
<td></td>
</tr>
<tr>
<td>Number of cycles of 2nd-line CT</td>
<td>9</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>1–40</td>
<td>1–5</td>
<td></td>
</tr>
</tbody>
</table>

ECOG = Eastern Cooperative Oncology Group, CT = chemotherapy, TMZ = temozolomide, BI = bevacizumab/irinotecan, PCV = procarbazine/lomustine/vincristine, RT = radiation therapy.
Second-Line Chemotherapy in Recurrent Glioblastoma

Fig. 1. Example of a complete response after BI treatment. Brain MRI (a, b, e, f: axial T2; c, g: axial T1 contrast-enhanced; d, h: T1 no contrast) of a 55-year-old patient with a left parietal GB upon recurrence (a–d) and after the 5th cycle of BI (e–h).

Fig. 2. (A) Overall survival curve of the PCV cohort. (B) Overall survival curve of the BI cohort. (C) PFS curve of the PCV cohort. (D) PFS curve of the BI cohort.

group, 65.9% had an OR, with 43.9% (n = 18) complete/partial response and 22.0% (n = 9) stable disease. Figure 1 illustrates an example of complete response with BI treatment. In contrast, in the PCV group, only 10.6% (n = 2) experienced OR, while the vast majority (78.9%, n = 15) had disease progression.

RANO Criteria

In the BI group, it was possible to assess the response by the RANO criteria in 37 patients (90.2%). The 4 patients who had no evaluation with the RANO criteria had stable disease based on the Macdonald criteria.

According to the RANO criteria, the rate of OR was 51.2% (n = 21) with 41.5% (n = 17) complete/partial response and 9.8% (n = 4) stable disease. 1 patient with partial response and 1 with stable disease, based on the Macdonald criteria, were considered to have disease progression based on the RANO criteria. The overall kappa statistics was 0.79 (95% CI 0.639–0.924, p < 0.001), indicating substantial agreement between the Macdonald and RANO criteria.
Survival Analysis

With a median follow-up time of 18.0 months (range 8–63 months), the median PFS time was 5 months (95% CI 3.8–6.2 months) for the BI group and 3 months (95% CI 1.0–5.0 months) for the PCV group. The PFS data are illustrated by the Kaplan-Meier curve in fig. 2a. 15 patients in the BI group were submitted to a third line of chemotherapy since they maintained a good performance status in spite of progression under BI.

The median OS from the beginning of second-line chemotherapy (fig. 2b) was 9.0 months (95% CI 0.0–18.8 months) in the BI group and 5.0 months (95% CI 4.2–5.8 months) in the PCV group. 1 year after beginning of second-line chemotherapy, 45.7% of the patients in the BI group were alive, in contrast to only 0.1% of the patients in the PCV group.

Safety Profile

All patients were included in the safety analysis (table 2). The PCV group experienced a worse toxicity profile. Almost 90% of the patients in the PCV group had grade 1–2 toxicities, contrasting with 68.3% in the BI group. Grade 3–4 toxicities were also more frequent in the PCV group (52.6% vs. 22.0%).

The main AEs in the BI group were neutropenia (24.4%, n = 10), thrombocytopenia (19.5%, n = 8), diarrhea (19.5%, n = 8), and proteinuria (17.1%, n = 7). 1 patient had CNS hemorrhage and 4 had venous thrombosis events (superficial or uncomplicated deep-vein thrombosis) (table 2).

Hematologic toxicity was more frequent in the PCV group: leukopenia (57.9%, n = 11), neutropenia (47.4%, n = 9), and thrombocytopenia (73.7%, n = 14).

Overall, in 12 patients, the second-line chemotherapy was suspended due to toxicity (8 in the BI group and 4 in the PCV group).

Progression Patterns

Within the BI group, 18 (43.9%) patients exhibited focal recurrence, 5 (12.2%) patients had multifocal progression, and 5 (12.2%) patients had non-enhancing progression. 6 (14.6%) patients had no progression, and in 7 (17.1%) patients it was not possible to determine the progression pattern. 11 (55.0%) patients in the PCV group presented focal recurrence, 6 (30.0%) had multifocal progression, and in 3 (15.0%) patients it was not possible to determine the progression pattern.

Regarding the treatment options after second progression, 15 patients (36.6%) in the BI group were able to receive a third-line chemotherapy. 6 patients received PCV, 8 were treated with continuous TMZ, and 1 patient was treated with the ICE regimen (ifosfamide/carboplatin/etoposide). In the PCV group, only 5 patients (26.3%) had third-line treatment: 2 patients received BI and 3 were treated with continuous TMZ.

Discussion

Malignant gliomas are highly vascular and express excess amounts of VEGF, which not only promotes tumor angiogenesis but
also decreases the bioavailability of chemotherapeutic drugs. Thus, the inhibition of VEGF may reduce angiogenesis and increase the delivery and effect of cytotoxic chemotherapy, namely irinotecan.

We observed not only an almost double median OS time in the BI group compared to the PCV group (9.0 vs. 5.0 months) but also a trend toward longer PFS in the BI group.

Several authors have raised the question of whether bevacizumab could alter the recurrence pattern of malignant gliomas by suppressing contrast-enhancing tumor recurrence more effectively than it suppresses non-contrast-enhancing, infiltrative tumor growth [13–15]. From this perspective, it is important to acknowledge the value of the RANO working group criteria which, in addition to other items, take into account the non-enhancing tumor by evaluating the T2/FLAIR signal [12]. The OR rate in the BI cohort, using the RANO criteria, was similar to that observed with the Macdonald criteria (51.2% vs. 65.9%), corresponding to a substantial agreement between the criteria. In contrast to this excellent RR with the BI combination, the OR rate of the PCV group was only 10.6%. The survival data regarding the PCV group (5 months OS, 3 months PFS) was also slightly inferior when compared to some literature data. The Medical Research Council (MRC) BR12 trial, which compares 2 regimens of TMZ to PCV in the setting of recurrent high-grade glioma, reports a median survival of 6.7 and 7.2 months for PCV and TMZ, respectively, and a median PFS of 3.6 months for PCV and 4.7 months for TMZ. This may be attributed to the fact that the MRC BR12 study included a significant number of World Health Organization (WHO) grade 3 tumors (51 in the PCV group and 52 in the TMZ group), while our cohort included exclusively GBs [16].

Our results are similar to those described in the literature for bevacizumab-containing chemotherapy [15, 17–23]. More recently, the BELOB trial has compared single-agent bevacizumab versus lomustine alone versus combined bevacizumab plus lomustine, showing a 9-month OS of 63%, with good tolerability with lomustine dose reduction. This trial suggests that the combination of bevacizumab and lomustine might have more activity than each drug administered alone. Nonetheless, until the results of a phase III trial are available, the activity of this combination in recurrent GB remains uncertain [24]. We eagerly await the results of the ongoing European Organisation for Research and Treatment of Cancer (EORTC) study 26101 (NCT01290939), with study completion expected by September 2015. Another recent randomized phase II study, the AVAREG trial, explored the efficacy of fotemustine versus bevacizumab in recurrent GB multiforme (GBM). Although not designed to be comparative, the 6-month OS and median OS proved to be better in the fotemustine arm [17].

In our study, a larger proportion of patients in the BI group experienced clinical benefit and most of the cases of disease progression were radiological findings, with patients retaining a good performance status that allowed those progressing under BI to be re-challenged with subsequent lines of chemotherapy (36.6%). In contrast, in the PCV group, most patients experienced clinical deterioration, which made it impossible to try a different line of chemotherapy. In this group, only 26.3% had further treatment. Also a significant number of patients reduced or discontinued corticosteroid therapy in the BI cohort, in contrast to no patient in the PCV cohort. The benefit of bevacizumab as a corticosteroid-sparing agent has been shown in other studies [15, 18].

The BI group had not only better results in terms of survival and OR but also a better safety profile with lower rates of grade 3–4 AEs. The BI combination was well tolerated, and the incidence of targeted AEs was similar to those observed in previous trials [15, 18, 19, 21, 25, 26]. The BI group experienced a higher incidence of venous thromboembolic events and the hematologic AEs were more frequent in the PCV-treated patients. Of note, the unexpected higher incidence of CNS hemorrhage in the PCV group was probably associated with the lower antitumor response and subsequent tumor progression.

Our data are limited mainly due to the small number of patients and the retrospective study design. Furthermore, the most recent patients were predominantly treated with BI, while most patients were treated with second-line PCV before institutional approval of anti-angiogenic treatment in this setting. The limited patient number illustrates not only the low frequency of this entity but also the poor prognosis, since only a proportion of these patients survive to first-line treatment and have a good enough performance status to be eligible for second-line approaches.

Another limitation of our study is the absence of O6-methylguanine methyltransferase (MGMT) promoter methylation determination, which is not implemented in our hospital due to the lack of therapeutic implications, with the exception of GB in elderly people. Effectively, the positive prognostic role of MGMT promoter methylation in GB patients treated with TMZ was confirmed prospectively in the Radiation Therapy Oncology Group (RTOG) 0525/EORTC/North Central Cancer Treatment Group Intergroup Study [27]. Nevertheless, the identical time to first progression with TMZ between groups may indicate that the proportion of methylation of this molecular factor is not very different between the cohorts.

In our study, we did not identify an exclusively invasive non-enhancing diffuse progression phenotype during bevacizumab treatment and most patients did not show a change from the initial pattern of recurrence after progression while on bevacizumab.

According to our results, the association of BI seems a valuable treatment option in recurrent GB, with a good safety profile. Prospective randomized controlled studies comparing these 2 therapeutic approaches are warranted.

**Ethical Standards**

This study was performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

**Disclosure Statement**

No conflicts of interest to declare.
References