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ORIGINAL ARTICLE

# Bevacizumab-containing regimen in relapsed/progressed brain tumors: a single-institution experience

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## Abstract

**Aim** The aim of the study is to assess tumor response, treatment-related toxicities, progression-free survival (PFS), and overall survival (OS) in patients with relapsed/refractory brain tumors treated with bevacizumab-containing regimen.

**Methods** Patients that had received I and II line treatments with or without megatherapy were included. Doses and schedule were as follows: bevacizumab (BVZ) 10 mg/kg i.v. with irinotecan (IRI) 150 mg/m$^2$ i.v. every 2 weeks ± temozolamide (TMZ) 200 mg/m$^2$ p.o. daily for 5 days every 4 weeks. TMZ was omitted in heavily pretreated cases.

**Results** Between 2013 and 2018, 12 patients (3F/9M), median age 161 months (range 66–348), affected with medulloblastoma (*n* 7), or low-grade glioma (*n* 2), or high-grade glioma (*n* 3), received BVZ/IRI association (median courses 20, range 4–67); 3 of them continued single-agent BVZ (median courses 23, range 8–39). TMZ (median courses 8, range 2–26) was administered in eight patients and then stopped in three of them because of myelotoxicity or lack of compliance. Treatment was well tolerated. After 3 months, two complete responses, two partial responses, seven stable diseases, and one progressive disease were observed. Nine cases experienced an improvement in neurological symptoms. Median time to progression was 11 months (95% confidence interval, 4–18 months). Six-month and 2-year PFS were 75% and 42%, respectively. The OS is 33%; interestingly, two cases (one medulloblastoma and one high-grade glioma) are progression-free off-therapy since 30 and 48 months, respectively.

**Conclusions** BVZ/IRI association ± TMZ showed encouraging therapeutic activity and low toxicity in this series of relapsed/refractory brain tumors.

**Keywords** Brain tumors · Children · Relapse · Irinotecan · Bevacizumab

## Introduction

Survival has improved for malignant central nervous system (CNS) tumors in children, but outcome for recurrent and/or refractory disease remains disappointing and most patients succumb to disease progression [1]. Salvage treatments include re-resection, re-irradiation, further lines of chemotherapy with or without megatherapy, according to the site, the histology, and the previous treatment. No single chemotherapy regimen has demonstrated significantly better results in the setting of disease relapse. Therefore, the development of new therapeutic strategies is required in order to increase survival for CNS tumor relapses. Among the new therapeutic strategies currently developed, drugs that target the neoplastic neovascularization have shown interesting results in some cases [2–8]. Tumor angiogenesis is an essential process promoting tumor growth, invasion, and metastasis. Vascular endothelial growth factor (VEGF) is a key angiogenesis mediator that is overexpressed in CNS tumors [9]. Bevacizumab (BVZ; Avastin, Genentech) is a humanized monoclonal antibody that is highly specific for all VEGF isoforms [10]. Anti-angiogenic strategies using BVZ have been successfully developed in adult cancers such as metastatic colorectal cancer and advanced non-small cell lung cancer [11, 12]. BVZ has been used in combination with irinotecan (IRI) in adult patients with high-grade glioma [13, 14]. The well-established dependence of pediatric tumors on the

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neovascularization and the encouraging clinical results obtained in some adult malignancies led to the use of BVZ in combination with cytotoxic drugs in children affected with relapsed or refractory CNS tumor [2–8]. Few pediatric studies have been published, so far [2–8]. Here, we report on our experience of BVZ/IRI ± temozolomide (TMZ) performed in a single center in order to evaluate the efficacy and toxicity of this regimen in patients affected with relapsed/refractory CNS tumor.

## Patients and methods

The objectives of the study were to estimate the rate of objective responses (ORs) (complete response [CR] + partial response [PR] + stable disease [SD]), the treatment-related toxicities, the progression-free survival (PFS), and the overall survival in children and young adults with relapsed/refractory CNS tumors.

### Eligibility criteria

Patients with recurrent or progressive histologically confirmed CNS tumor based on centralized pathology review (those with visual pathway tumors or intrinsic brainstem tumors did not need histological confirmation) that had received I and II line treatments with or without high-dose chemotherapy and autologous stem cell transplantation were considered eligible for salvage treatment with bevacizumab-containing regimen. Patients were required to have a Karnofsky or Lansky score of at least 60, to be ≥ 3 weeks from prior myelosuppressive chemotherapy, and to be ≥ 4 weeks from prior major surgical resection and ≥ 3 months from local radiotherapy. Written informed consent was given by the patient or the patient's parents. The enrollment of the patients was approved by the local ethical institutional committee.

Clinical and laboratory examinations prior to the first administration of BVZ included blood pressure measurement, performance status, echocardiography and electrocardiography, full blood cell count, and assessment of electrolyte disorders, liver and renal function (including proteinuria), and hemostasis parameters.

### Doses and schedule

BVZ was administered intravenously at a dose of 10 mg/kg in combination with intravenous IRI, at a dose of 150 mg/m$^2$. BVZ/IRI association was given every 14 days. TMZ was added orally at a dose of 200 mg/m$^2$/day for five consecutive days every 28 days, but it was omitted in heavily pretreated patients because of previous delays in bone marrow recovery, and it was stopped in the cases who experienced hematological toxicity > IV grade WHO or lack of compliance. Blood tests were done in all patients prior each course and 7 days after starting therapy. Stop therapy criteria for the association of BVZ/IRI association were as follows: hematologic toxicity > IV grade WHO, disease progression, worsening of clinical general conditions, and neurological symptoms.

### Response and toxicity assessment

Tumor response was assessed based on institutional radiology review of the MR imaging and defined as complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the Response Assessment in Neuro-Oncology criteria and the Response Assessment in Pediatric Neuro-Oncology (15, 16).

Response was assessed at the time of initiation of salvage treatment, and every 3 months thereafter until tumor progression. Patients were also considered to have PD if they had clear neurological deterioration, even without a definitive evidence of tumor growth on MRI of the brain and spine.

Side effects were retrospectively collected and categorized according to the Common Terminology Criteria for Adverse Events Version 4.0.

### Statistical considerations

Progression-free survival (PFS) was defined as the time between starting therapy and disease progression, and it was calculated using the Kaplan-Meier method.

## Results

### Patients

A total of 12 patients (3 females and 9 males) were enrolled between 2013 and 2018. Patient characteristics are listed in Table 1. The median age at diagnosis was 133 months (range 17–312); the median age at the BVZ-containing regimen administration was 161 months (range 66–348). Three patients were young adults (> 18 and < 29 years old).

Seven patients had medulloblastoma (MB), two patients had low-grade glioma (LGG), and one of these being affected with neurofibromatosis I. Three patients had high-grade glioma (HGG): glioblastoma (2 pts) and anaplastic astrocytoma grade III WHO (1 pt).

Karnosky or Lansky score was assessed in all patients, and the median value was 80 (range 60–100).

All patients received at least six BVZ/IRI courses (median 20, range 6–67); three of them continued therapy with single-agent BVZ (median courses 23, range 8–39). TMZ was omitted in four heavily pretreated patients; thus, TMZ was given to eight patients in combination with BVZ/IRI, and in three of them, it was stopped because of myelotoxicity and/or lack of

**Table 1** Characteristics of patients

| Pt | Gender | Age D (mos) | Age S (mos) | Histology | Previous therapy | Relapse | Performance status (%) | Response after 3 mos | Time to progression (mos) | Status |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 41 | 66 | Classic MB | S, cranio-spinal RT, CHT (CBDCA/VP16; VCR/CYCLO; MTX), HDCT (thiotepa) | 2° | 90 | CR | – | NED off-therapy 30 mos |
| 2 | F | 148 | 170 | Anaplastic MB | S, cranio-spinal RT, CHT (CBDCA/VP16; VCR/CYCLO; MTX), HDCT (thiotepa) | 1° | 90 | PD | 2 | Dead |
| 3 | M | 131 | 152 | Anaplastic MB | S, cranio-spinal RT, CHT (CBDCAVP16; /VCR/CYCLO; MTX) | 1° | 90 | SD | 9 | Dead |
| 4 | F | 135 | 145 | GB | S, local RT, CHT (TMZ; CBDCA/VP16) | 2° | 80 | SD | 7 | Dead |
| 5 | M | 72 | 91 | Classic MB | S, cranio-spinal RT, CHT (CDDP/VCR/CCNU; CBDCA/VP16), HDCT (thiotepa) | 2° | 90 | SD | 4 | Dead |
| 6 | M | 127 | 146 | PNET | S, cranio-spinal RT, CHT (CBDCA/VP16; gemcitabine/oxaliplatin) | 2° | < 70 | SD | 5 | Dead |
| 7 | M | 238 | 300 | Classic MB | S, cranio-spinal RT, CHT (CBDCA/VP16; CYCLO/VCR; CDDP), HDCT (thiotepa) | 3° | 80 | CR | 24 | AWD under different therapy |
| 8 | M | 17 | 72 | LGG + NF1 | S, CHT (CBDCA/VCR) | 2° | < 70 | PR | 43 | AWD under different therapy |
| 9 | M | 300 | 348 | LGG (gliomatosis cerebri) | S, RT, intrathecal CHT | 3° | < 70 | PR | 45 | Dead |
| 10 | F | 312 | 318 | HGG (anaplastic astrocytoma grade III WHO) | Biopsy, local RT | 1° | 90 | SD | – | NED off-therapy 48 mos |
| 11 | M | 126 | 196 | Classic MB | S, cranio-spinal RT, CHT (CBDCA/VP16; VCRCYCLO; MTX), HDCT (thiotepa) | 1° | 90 | SD | 8 | Dead |
| 12 | M | 262 | 312 | GB | S, local RT | 1° | 90 | SD | 10 | Dead |

*Pt* patient, *D* diagnosis, *S* study, *mos* months, *MB* medulloblastoma, *PNET* primitive neuroectodermal tumor, *LGG* low-grade glioma, *NF1* neurofibromatosis 1, *HGG* high-grade glioma, *GB* glioblastoma, *CHT* chemotherapy, *CBDCA* carboplatin, *VP16* etoposide, *VCR* vincristine, *CYCLO* cyclophosphamide, *CDDP* cisplatin, *TMZ* temozolomide, *RT* radiotherapy, *S* surgery, *HDCT* high-dose chemotherapy, *CR* complete response, *PD* progressive disease, *SD* stable disease, *PR* partial response, *NED* no evidence of disease, *AWD* alive with disease

compliance (median courses of TMZ 8, range 2–26). No dose adjustment was made for patients receiving antiepileptic drugs.

### Response and survival

After 3 months, two CRs, two PRs (Fig. 1a, b), seven SDs, and one PD were registered at MRI (Table 1). The rate of major responses (CR + PR) was 33.3%; the rate of OR was 92%. A significant improvement in neurological symptoms was also observed in 80% of the patients. The median PFS following initiation of therapy was 11 months (95% confidence interval (CI), 4–18 months). The 6-month and 2-year PFS rates were 75% and 42%, respectively (Fig. 2). Currently, OS is 33.3%. Interestingly, two cases are progression-free off-therapy since 30 and 48 months, respectively.

One of these (patient no. 10 in Table 1) was a patient with anaplastic astrocytoma grade III who was treated at onset with biopsy and a stereotactic radiosurgery by the CyberKnife system. After 6 months, the deterioration in neurological symptoms and the enlarged lesion using advanced diffusion MRI sequences allowed to a diagnosis of tumor progression. BVZ/IRI/TMZ was started, and a stable disease was documented after 3 months; thus, a second stereotactic radiosurgery was delivered, and BVZ/IRI/TMZ therapy was continued for further 7 months obtaining a complete response. The patient received a total of 19 administrations of BVZ/IRI and 10 of TMZ. At present, the patient is alive in complete remission off-therapy for 48 months.

The other one (patient no. 1 in Table 1) was a 41-month boy affected with high-risk classic medulloblastoma, who was treated with subtotal resection, chemotherapy, craniospinal irradiation, and megatherapy with thiothepa. He presented with first local relapse after 12 months, and he was re-treated with second surgery and further chemotherapy obtaining a second complete remission. After further 12 months, the boy presented with a second distant relapse with a gross nodule in the spinal subarachnoid space at C7 level and a spinal leptomeningeal involvement at L2-S5 levels at MRI; he was treated with a surgical removal of the spinal subarachnoid gross nodule (histology confirmed a classic medulloblastoma) followed by bevacizumab-containing regimen for a total of 3 years and 10 months. A complete disappearance of leptomeningeal involvement was documented at MRI, after 3 months. Fifty-two courses of BVZ/IRI every 2 weeks and 26 courses of TMZ every 4 weeks were administered followed by 15 courses of BVZ/IRI every 28 days. In the last year, the patient received a monthly single-agent bevacizumab for eight courses. At present, he is alive in complete remission off-therapy for 30 months.

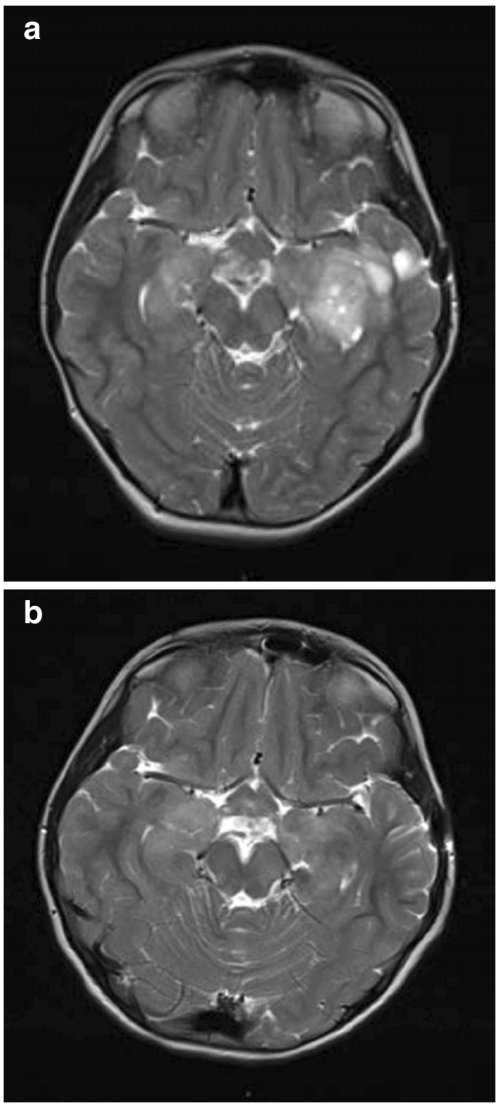


**Fig. 1** **a** Brain magnetic resonance in LGG patient with neurofibromatosis type 1. **b** Brain magnetic resonance in LGG patient with neurofibromatosis type 1 after 3 months of therapy with bevacizumab and irinotecan

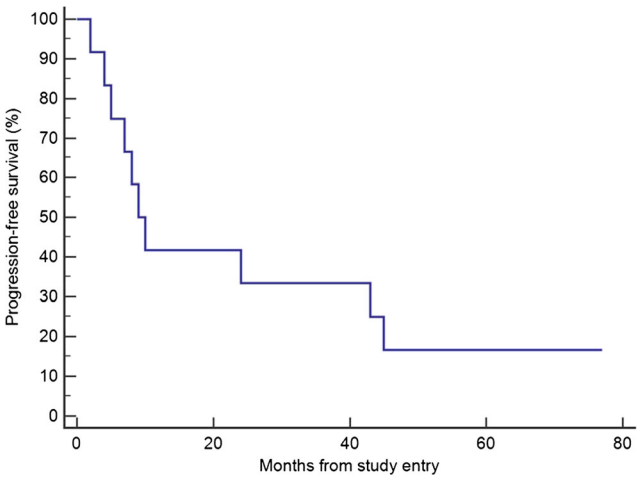


**Fig. 2** Progression-free survival for patients affected by relapsed/refractory brain tumors treated with bevacizumab-containing regimen

The remaining two surviving patients are being treated with a different therapy after progression with bevacizumab-containing regimen.

### Toxicity

Treatment was well tolerated, and it was associated with a good quality of life. No alopecia was observed. Two cases had a mild hypertension. In four patients, grade 2 nausea and vomiting were reported with prompt benefit after antiemetic drugs. In six patients, grade 2 diarrhea occurred, both within a few hours after therapy and in the time interval between subsequent administrations. Diarrhea responded to the administration of oral cefixime. Five patients developed grade 3 thrombocytopenia; one patient developed grade 3 anemia; in one patient, grade 4 hematologic toxicity was observed. Two patients had allergic reaction with hives and cough resolved after antihistamine drugs administration. Finally, three patients experienced headache after the administration of the therapy, and four cases had grade 1 proteinuria. There were no toxicity-related deaths. In the patients off-therapy, the toxicities including the proteinuria were quickly reversible on drug withdrawal.

## Discussion

The present study in recurrent/refractory CNS tumors in children and young adults has shown that BVZ + IRI ± TMZ is an effective combination in producing an objective response rate in 92% of the patients who had previously failed standard radiotherapy and/or chemotherapy. A significant improvement in neurological symptoms was also observed in 80% of the patients. Importantly, one case affected with MB and another one with anaplastic astrocytoma are alive without disease progression after 30 and 48 months, respectively, from the stop therapy. They also benefited from surgery and radiotherapy, respectively, but these two therapeutic tools had previously been used without being able to prevent the relapse. These results, although obtained in a limited series of patients, suggest that this regimen may play an important role in a subtype of patients.

In general, IRI has been reported to have only a limited efficacy in both adult and pediatric brain tumors [17]. In a phase II study of single-agent irinotecan in children with recurrent CNS tumors, no objective responses were observed [18]. Couec et al. tested the efficacy and toxicity of IRI associated with BVZ in children with recurrent or refractory brain tumors: some efficacy was observed in patients with LGG, while no activity was documented in patients with HGG, PNET, or ependymoma [2]. Other studies confirmed the efficacy of BVZ/IRI therapy in pediatric patients with LGG, which had already been treated with first- and second-line therapies or which could not undergo radiotherapy because of young age or lesion site [3–5]. In particular, in the Packer et al. study, the rate of major responses was 40%, and an improvement of neurological symptoms was also observed [3]. Aguilera et al. tested the efficacy of BVZ/IRI association ± TMZ in patients affected with relapsed medulloblastoma [6]. They obtained an objective response rate of 55% at 6 months from the start of therapy; three children with relapsed medulloblastoma remained alive 15 to 55 months following salvage therapy, two of them progression free. Bonney et al. reported an excellent response to BVZ/IRI/TMZ in a 20-year-old patient affected with relapsed MB and metastatic bone lesions [18]. On the other hand, the clinical experience with BVZ/IRI association in pediatric patients with HGG is more limited and controversial [7, 8, 19]. Although BVZ is approved for the use in adults with first glioblastoma recurrence and it may be of clinical benefit in newly diagnosed patients with unresectable disease [20], the addition of BVZ in children with malignant glioma demonstrated limited activity, so far [21, 22].

In the present study, the response rates and progression-free survival that we obtained using BVZ/IRI regimen in cases affected with different types of brain tumors are similar to those observed in other previous studies evaluating the therapeutic activity of salvage chemotherapy in recurrent/refractory disease. Objective responses have also been described after therapy with a variety of different drugs such as cisplatin, carboplatin, etoposide, and cyclophosphamide [1]. However, even though the present regimen of BVZ/IRI association with or without TMZ did not produce better results in terms of tumor response rates, it is interesting to note that two patients are long-term survivors. Further studies in more numerous series will be needed to confirm whether this regimen can actually induce a long-term response in a subset of patients.

In our experience, this regimen seems to be associated with very favorable results in terms of quality of life. The toxicity was mild and easily controlled, even though most of patients were heavily pre-treated and underwent long-term therapy. Fangusaro et al. reported the toxicities of BVZ/IRI regimen in 92 patients [23]. The most common side effects were proteinuria, hypertension, fatigue, and epistaxis. Therapy had to be discontinued do to the toxicity in 24% of patients. The authors concluded that the association of the two drugs is well tolerated and serious side effects rarely occurred. More importantly, severe toxicities related to BVZ were quite rare and quickly reversible on drug withdrawal [22]. Therefore, the BVZ/IRI regimen may represent a valid strategy in the palliative therapy setting, especially since patients with relapsed brain tumor are usually rather frail and require tolerable therapies, which can still ensure a good quality of life. Should a significant therapeutic activity be confirmed in such a subset of patients, the possibility of integrating BVZ in first-line regimen might also require to be assessed.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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