Child's Nervous System
https://doi.org/10.1007/s00381-021-05138-3

ORIGINAL ARTICLE

Targeted therapy for pediatric low-grade glioma

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Received: 18 November 2020 / Accepted: 17 March 2021

Abstract

Purpose Pediatric low-grade gliomas are the most frequent brain tumors in children. The standard approach for symptomatic unresectable tumors is chemotherapy. Recently, key molecular alterations/pathways have been identified and targeted drugs developed and tested in clinical trials. We describe our institutional experience with MAPK pathway targeted therapy.

Methods We retrospectively reviewed the medical reports of 23 patients diagnosed with PLGG and treated with either trametinib or dabrafenib at Hospital Sant Joan de Dèu (Barcelona, Spain). Patients with neurofibromatosis were excluded. Objective response rate (ORR) and disease control rate (DCR) were determined using the Response Assessment in Pediatric Neuro-Oncology criteria in low-grade glioma. ORR was defined as the proportion of patients with the best overall response including complete remission (CR) or partial remission (PR). DCR was the sum of the CR, PR, and stable disease (SD) rates.

Results ORR with trametinib was 0% (95% CI, 0%–23.2%) and DCR was 78.6% (95% CI, 49.2%–95.3%). Eleven patients had SD and three patients presented PD. ORR with dabrafenib was 41.7% (95% CI, 16.5%–71.4%), including four CR and one patient with PR. DCR with dabrafenib was 100% (95% CI, 73.5%–100%); there were seven SD and none PD. Treatment was well tolerated. Only three patients, on trametinib, presented grade 3 adverse effects: leukocytoclastic vasculitis, cheilitis, and bone infection.

Conclusions Our experience adds to the growing data about the efficacy and tolerability of targeted therapy in patients with PLGG. When present, toxicity is mainly mild-moderate and transient. Ongoing prospective clinical trials are trying to address if its use should be advanced to first-line therapy.

Keywords Pediatric low-grade gliomas · MAPK pathway · Targeted therapy · Trametinib · Dabrafenib

Introduction

Pediatric low-grade gliomas (PLGG) constitute the largest group of tumors occurring throughout all pediatric age groups and in the central nervous system. When located in the posterior fossa or in accessible areas of brain and spinal cord, gross total resection (GTR) is the treatment of choice. If this is achieved, no further therapy is indicated and prognosis is usually excellent.

However, a significant number of these lesions involve eloquent areas including the optic chiasm, optic pathway, or deep midline structures within the neuroaxis, locations not amenable to complete resection without major neurologic sequelae. Thereafter, these cases require adjuvant therapies for tumor control [1]. Historically, irradiation and chemotherapy have been used to achieve this objective. The response obtained with both approaches is similar achieving at best partial responses or tumor stability. Additionally, irradiation has been shown to be associated not only with middle- and long-term significant neurology toxicity but also with increased mortality in long-term survivors [2, 3]. On the other hand, conventional adjuvant chemotherapy regimens used for these conditions, although less toxic, imply frequent visits to the oncology clinic, central line access and may have adverse events. Moreover, it is not unusual that patients with tumor residual

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Published online: 17 April 2021

at the end of chemo or radiotherapy will develop a new progression months or years after therapy discontinuation. Therefore, unresectable PLGG should be seen as a chronic condition with the same patient needing more than one therapeutic regimen to achieve long-term tumor control [4]. PLGG comprises a heterogeneous group of histologic entities. Importantly, molecular characterization has shown us that the vast majority of these tumors are associated with one of a variety of alterations in the mitogen-activated protein kinase (MAPK) signaling pathway, including the *BRAF* tandem duplication or V600E mutation [5].

In brief, *BRAF* is an intermediary in the RAS-RAF-MEK-ERK MAPK signaling pathway. It serves different roles including cell cycle arrest, cell proliferation, differentiation, and apoptosis. A tandem duplication of ~2 Mb at 7q34 causing the fusion of two genes, the N-terminal of *KIAA1549*, replaces the regulatory region of *BRAF*, resulting in a constitutively activated protein (BRAF-KIAA1549). The deregulated *BRAF* activity leads to increased downstream signaling (MEK/ERK) and subsequent increased cell proliferation. On the other hand, the majority of reported *BRAF* mutations occur as a single amino acid substitution in exon 15 at the residue 600. This results in constitutive activation of BRAF´s kinase function [1, 6–8].

Interestingly, the presence of these genetic alterations is related to the histology, prognosis, and location of the tumor. For example, the *BRAF-KIAA1549* fusion is more common in pilocytic astrocytoma (PA) than in other PLGG, being particularly common in the cerebellum [5]. On the other hand, mutation screening studies have revealed that *BRAF V600E* frequencies are higher in pleomorphic xanthoastrocytoma (PXA) and ganglioglioma located in cerebral hemispheres [5, 9]. Retrospective multi-institutional studies have revealed that tumors harboring the *BRAF V600E* are biologically more aggressive and have worse prognosis in comparison with tumors harboring the *BRAF* tandem duplication [10]. Furthermore, tumors with *CDKN2A* alteration have an even worse prognosis and risk of malignant transformation [11].

There is an increasing experience showing that targeted therapy such as BRAF inhibitors (in tumors with *BRAF V600E* mutant) and MEK inhibitors (in tumors with the tandem duplication) are effective in PLGG [12–14].

Here, we describe the efficacy and safety of targeted therapy in 23 patients with PLGG and *KIAA1549-BRAF* fusion or *BRAF V600E* mutant treated in our institution.

Methods

We retrospectively reviewed the medical reports of patients diagnosed with PLGG and treated with either trametinib or dabrafenib at Hospital Sant Joan de Dèu (Barcelona, Spain). Both drugs were obtained under a compassionate use program and informed consent was signed prior to starting the treatment. We included demographic data, tumor location, histology, previous treatment(s), duration of treatment with targeted therapy, reported adverse effects (AEs), and treatment response. Patients with PLGG of any histology with *BRAF V600E* or *KIAA1549-BRAF* fusion were included. Patients with other abnormalities of the MAPK pathway or with neurofibromatosis type 1 were excluded. All tumors were analyzed in order to identify *BRAF* status. *BRAF V600E* and *KIAA1549-BRAF* fusion were determined by RT-qPCR. *CDKN2A* deletion was evaluated by multiplex ligation-dependent probe amplification. For the evaluation of the AEs during the treatment we used the "Common Terminology Criteria for Adverse Events (CTCAE) v5.0."

Patients with the tandem duplication were treated with trametinib (dose: 0.025 mg/kg/day, every 24 h) and patients with the *BRAF* mutation with dabrafenib (dose: 5.25 mg/kg/day, every 12 h). The doses are in line with the published recommended doses for pediatric patients [14–16].

The objective response rate (ORR) and disease control rate (DCR) was determined using the Response Assessment in Pediatric Neuro-Oncology (RAPNO) criteria in low-grade glioma [17]. The ORR was defined as the proportion of all treated patients with the best overall response including complete remission (CR) or partial remission (PR). The DCR was the sum of the CR, PR, and stable disease (SD) rates. Ninety-five-percent confidence intervals (CI) were estimated for the results of these variables. Progression-free survival (PFS) was estimated by Kaplan-Meier analysis.

All magnetic resonance imaging (MRI) studies were acquired on either a 1.5-T General Electric Signa HD scanner or a 3-T Philips Ingenia scanner. All studies included a 3D T1, 3D FLAIR, DWI, FSE T2, SWI, and contrast administration. Tumor size changes were assessed by linear analysis. Measurements were performed with Philips IntelliSpace Portal software version 10.1 (CE approved, FDA 510(k) clearance). Tumor margins were delineated in 3D T1 or 3D FLAIR images—depending on tumor enhancement and signal intensity—with a semiautomatic approach that was manually corrected in each slice in the axial plane. Linear measurements in the axial plane (maximal tumor diameter and the perpendicular diameter) were performed in the same sequence. We assessed tumor response analyzing changes in the product of the two diameters (mm^2).

This study was approved by our institutional review board and research ethical committee.

Results

From December 2015 to February 2020, 23 patients (11 females) were treated with either trametinib or dabrafenib. Median age at diagnosis was 3.2 years (range: 0.4–17.8). Median age of the patients treated with trametinib was 1.6

years (range: 0.4–5.9) and with dabrafenib was 6.2 years (range: 0.5–17.8). The list of diagnosis by histopathology included: PA (n = 14), pilomyxoid astrocytoma (n = 5), ganglioglioma (n = 3), and PXA (n = 1).

The follow-up period was until June 30, 2020. The mean follow-up from the beginning of the targeted therapy was 25.6 months (range: 4–54). Prior to starting targeted therapy, 21 patients had presented a documented progression. Two patients started dabrafenib after initial diagnosis. Eighteen patients were previously treated with at least one line of chemotherapy (range 1–4).

Fourteen patients, with the tandem duplication, were treated with trametinib and 9 patients, with the *BRAF* mutation, with dabrafenib. Moreover, cases 16 and 23 presented *CDKN2A* deletion.

Trametinib was started at a median time from diagnosis of 60 months (range: 14–136) and was administered for 12 months on average (range: 6–21). Currently, six patients continue on trametinib. Three patients (21.4%) discontinued because of progressive disease (PD), one patient due to poor treatment efficacy (without radiological criteria of PD), and none because of AEs.

Nine patients were treated with dabrafenib. In total 12 courses of treatment were given. Seven patients received 1 course, 1 patient received 2 courses, and the other patient received 3 courses. It was started at a median time from diagnosis of 9 months (range: 1–59) and was administered for 15 months on average (range: 4–27). Currently, eight patients continue on dabrafenib. No patient discontinued because of disease progression or AEs.

Overall response is shown using waterfall plot (Fig. 1). ORR with trametinib was 0% (95% CI, 0%–23.2%) and DCR was 78.6% (95% CI, 49.2%–95.3%). Eleven patients had SD and three patients developed PD. The median PFS with trametinib was 38.2 months (95% CI: 35.3 months—not estimable), and the proportion of patients with PFS at 1 year of trametinib treatment was 84.6% (95% CI, 67.1%–100%). Three patients presented clinical improvement (Table 1: cases 3, 6, and 10).

ORR with dabrafenib was 41.7% (95% CI, 16.5%–71.4%), including one patient with PR and two patients with CR. One of them was treated with 3 courses of dabrafenib, due to PD after its suspension, achieving CR every time. DCR was 100% (95% CI, 73.5%–100%). Six patients presented SD (one of them achieved SD in two courses of treatment) and none had PD. The median PFS with dabrafenib was 26.1 months (95% CI: 25.5 months—not estimable), and the proportion of patients with PFS at 1 year of dabrafenib treatment was 100% (95% CI, 100%–100%). In five patients there was clinical improvement (Table 2: cases 15, 17, 18, 20, and 21), including visual function in two of them.

All patients presented mild skin toxicity. AEs responded well with supportive care, dose reduction, or discontinuation of treatment. Only three patients presented serious AEs and were grade 3; all of them identified on trametinib treatment: leukocytoclastic vasculitis, cheilitis, and a bone infection due to *Staphylococcus aureus*, all resolved after temporarily discontinuing trametinib. Thirteen patients presented mild laboratory abnormalities (CTCAE ≤ 2) including CPK, AST, ALT, AP, and/or LDH elevation above normal range. No ophthalmologic or cardiac

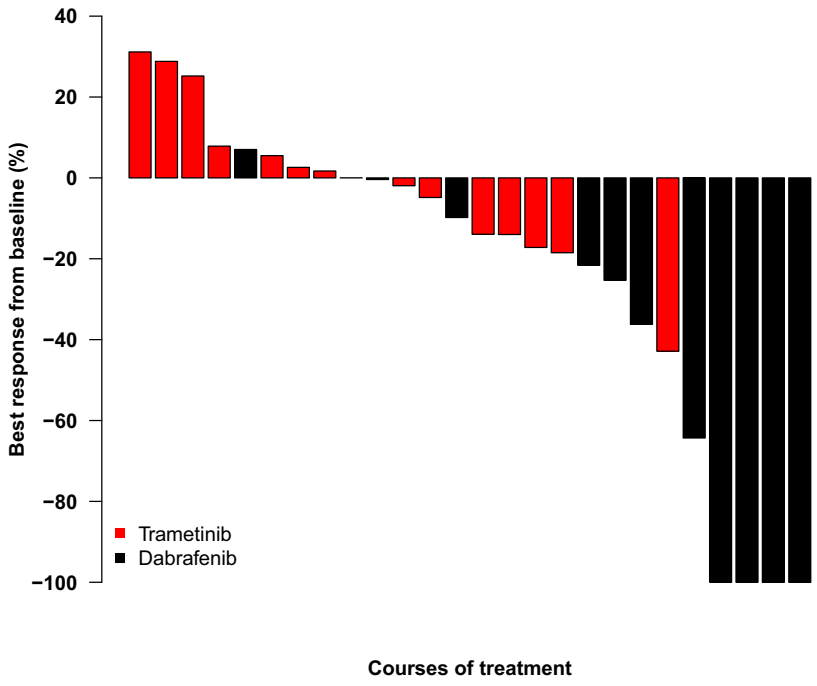

Fig. 1 Best overall response in all courses of treatment, using the RAPNO criteria in low-grade glioma. Each bar represents a course of treatment. Fourteen patients were treated with trametinib. Nine patients were treated with dabrafenib, although in 12 courses of treatment (4 CR were achieved with dabrafenib in 2 patients)

Table 1 PLGG with KIAA1549-BRAF fusion: patient characteristics, response, and toxicity with trametinib

Cases	Age at diagnosis (years); sex	Histologic diagnosis; tumor location	Prior surgery	Prior therapy	Age on treatment onset (years)	Time on treatment (months)	Best overall response	Functional response	Side effects
Case 1	1.5; F	PA; medulla oblongata with leptomeningeal dissemination	Biopsy	CPT 11-CDDP; VBL	5.8	20	PR	Stable	Skin (grade II) Abdominal pain (grade II) Cheilitis (grade I) CPK and AP increased (grade I)
Case 2	0.5; M	PMA; hypothalamic-chiasmatic	Biopsy, PR	VCR-CBCDA; 5 DR-BEV	1	18	SD	Stable	Skin (grade I) Cheilitis (grade I)
Case 3	0.9; F	PA; intramedullary	Biopsy	VCR-CBCDA; CPT 11-CDDP	12	15	SD	Improvement of brachial hemiparesis, resolution of paresthesia in hands and torticollis	Skin (grade II) Alopecia (grade I) Vasculitis (grade III) CPK and ALT increased (grade I)
Case 4	1; M	PMA; hypothalamic-chiasmatic	Biopsy	CPT 11-CDDP; VBL; BEV-CDDP; BEV	7.5	5	SD	Stable	Skin (grade II) Cheilitis (grade I) Mucositis oral (grade I) Abdominal pain (grade I) Fatigue and anorexia (grade II) CPK increased (grade I)
Case 5	4.4; F	PA; hypothalamic-chiasmatic	Biopsy, PR	CPT 11-CDDP; VBL; BEV-CDDP	12.5	8	PD	Visual deterioration	Skin (grade II) Alopecia (grade II) Cheilitis (grade III) Mucositis oral (grade II) Fatigue and anorexia (grade II)
Case 6	5.8; F	PA; intramedullary	Biopsy, PR	CPT 11-CDDP; VBL; BEV-CDDP	12.3	15	SD	Resolution of paresthesia in hands	Skin (grade I) Alopecia (grade I) Mucositis oral (grade I) CPK and LDH increased (grade I)
Case 7	0.8; F	PMA; hypothalamic-chiasmatic	Biopsy	VCR-CBCDA; BEV	2.8	6	PD	Stable	Skin (grade II) Alopecia (grade I) Abdominal pain (grade I)
Case 8	1.8; M	PAs; hypothalamic-chiasmatic	Biopsy	VCR-CBCDA; VBL	2.9	6	PD	Increased hemiparesis and cranial nerve abnormalities	Skin (grade I)
Case 9	3.9; M	PA; hypothalamic-chiasmatic with leptomeningeal dissemination	PR	CPT 11-CDDP	9.6	14 (continue)	SD	Stable	Skin (grade II) Abdominal pain (grade I) CPK increased (grade II) AST and LDH increased (grade I)
Case 10	0.4; M	PMA; hypothalamic-chiasmatic	Biopsy PR	VCR-CBCDA; VBL-BEV	1.8	14 (continue)	SD	Diencephalic syndrome improvement	Skin (grade II) Abdominal pain (grade II) Vomiting (grade I) CPK increased (grade II)
Case 11	1.1; F	GG; intramedullary	Biopsy, PR	CPT 11-CDDP; VBL; VCR-CBCDA; BEV-CPT 11	10.8	12 (continue)	SD	Stable	Skin (grade I) Cystitis (grade II) Lymph gland infection (grade III) LDH increased (grade I)

Table 1 (continued)

Cases	Age at diagnosis (years); sex	Histologic diagnosis; tumor location	Prior surgery	Prior therapy	Age on treatment onset (years)	Time on treatment (months)	Best overall response	Functional response	Side effects
Case 12	3.2; F	PMA; hypothalamic-chiasmatic	PR	CPT 11-CDDP; VBL	9.8	11 (continue)	SD	Stable	Skin (grade II) Alopecia (grade I) Abdominal pain (grade I) ALT, AST, AP and LDH increased (grade I)
Case 13	3.9; M	PA; tectal with leptomeningeal dissemination	Biopsy	No	8.1	10 (continue)	SD	Stable	Skin (grade II) Mucositis oral (grade I) Bone infection (grade III) Fatigue (grade II) Anorexia (grade I) Abdominal pain (grade I) CPK increased (grade 1)
Case 14	2.6; M	PA; hypothalamic-third ventricle	PR	VCR-CBCDA	5.5	6 (continue)	SD	Stable	Skin (grade II) Mucositis oral (grade II) Abdominal pain (grade I) Anorexia and fatigue (grade II) ALT, AST, AP, and CPK increased (grade I)

AP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BEV* bevacizumab, *CBCDA* carboplatin, *CDDP* cisplatin, *CPK* creatine phosphokinase, *F* female, *GTR* grow total resection, *GG* ganglioglioma, *LDH* lactate dehydrogenase, *M* male, *PA* pilocytic astrocytoma, *PD* progressive disease, *PMA* pilomyxoid astrocytoma, *PR* partial remission, *PXA* pleomorphic xanthoastrocytoma, *SD* stable disease, *VBL* vinblastine, *VCR* vincristine, *5DR* five-drug metronomic regimen

toxicities were identified. Few hospital visits were necessary for routine follow-up and patients were able to perform normal daily activities. All patients remain alive.

The main characteristics of the patients are depicted in Tables 1 and 2. In addition, we present 2 representative cases:

Patient 1

A previously healthy 6-month-old girl was initially diagnosed with a left temporal lobe lesion due to epilepsy. At age 3.5, GTR was performed due to lesion growth and drug resistant epilepsy. Histologic review was compatible with a PXA; *BRAFV600E* mutation and *CDKN2A* deletion were identified. Six months later, the patient developed a non-resectable asymptomatic local relapse. At that point, it was decided to start dabrafenib. An early MRI showed complete response after 4 weeks of therapy and at 6 months on therapy brain imaging showed no evidence of disease, maintaining the treatment for 10 months with good tolerance. Three months after discontinuing dabrafenib brain imaging showed a new asymptomatic relapse in the same location. It was decided to re-challenge with dabrafenib monotherapy, showing again complete response 3 months later, maintaining the treatment for 24 months. Two months after stopping treatment, she presented a new relapse, so dabrafenib was restarted with a new complete remission at 6 months. Currently, patient is on therapy with no evidence of disease and with no AEs from the medication (Fig. 2).

Patient 2

A previously healthy 14-year-old presented with headaches, vomiting, and crural paresis. A solid/cystic contrast enhancing thalamic-mesencephalic tumor was identified on the MRI. Due to the finding of hydrocephalus, a third ventriculostomy was performed with resolution of all symptoms. Given the potential morbidity of a surgical biopsy in an asymptomatic patient and the high clinical-radiological suspicion of PLGG, it was decided to start VCR/carbo without tumor biopsy. Six months later, due to asymptomatic tumor progression, therapy was switched to bevacizumab. Nine months into therapy, due to a new tumor progression, it was decided to perform biopsy and cystic fenestration. The histologic review confirmed a PA and molecular characterization confirmed the *BRAF V600E* mutation. After the procedure, dabrafenib was started with complete remission after 12 months on drug with good tolerance. Currently, patient is on therapy with no evidence of disease and with no AEs from the medication (Fig. 2).

Discussion

In the last years, novel drugs targeting the MAPK pathway through overactive *BRAF* have been introduced in the treatment of PLGG, including *BRAF* inhibition targeting the V600E mutation, and MEK inhibition by blocking the pathway activation downstream from the tandem duplication. These targeted drugs have opened a new possibility to treat patients who do not respond to standard regimens (i.e., chemotherapy), with the promise of increase effectiveness and less toxicity than with standard approaches. In this study, we report 23 cases of PLGG treated with targeted therapies, a potential new paradigm in the management of pediatric brain tumors.

A number of publications have shown institutional and collaborative experiences with these drugs [12–14, 16, 18, 19]. Selt et al. analyzed 18 patients treated with trametinib for progressive PLGG. Disease control rate was 100% under therapy [19]. Hargrave et al. demonstrated efficacy and safety of dabrafenib in patients with *BRAF V600*-mutant relapsed or refractory PLGG in a clinical trial, with radiological response in the majority of patients [14]. Nobre et al. reported 56 patients with PLGG *BRAF V600*-mutant treated with dabrafenib; objective responses were observed in 80% [18].

The vast majority of our cohort had radiologic response, except in three patients that progressed during therapy with trametinib. In addition, in two patients who relapsed after discontinuing dabrafenib, tumors responded again after re-challenging with the same drug. Of note, one of them (case 16) responded 2 times after taking the patient to complete remission after early relapses, even with the potentially unfavorable molecular prognosis of *CDKN2A* deleted concomitantly with *BRAFV600E* mutation in her tumor. Also, eight patients presented clinical improvement.

As reported previously, the most dramatic responses were observed in patients with *BRAF V600E* mutation [13, 14], highlighting clinical improvement in 5 patients treated with dabrafenib (Table 2: cases 15, 17, 18, 20, and 21), including visual acuity in two of them. Importantly, four patients were treated with dabrafenib upfront. Responses to chemotherapy in "non-pilocytic astrocytoma" PLGGs is not optimal. Therefore, given the more rapid response observed inhibiting the BRAF mutation, we opted for targeted therapy instead of the standard chemotherapy approach [10, 14, 18] (Table 2: cases 15, 16, 21, and 23). The results in these patients were favorable, with two patients present SD, one CR and another PR.

Based in published data and in our results, it seems more advantageous to start treatment with dabrafenib earlier in children with recurrent or progressive *BRAF V600E* mutant PLGG compared to trametinib in cases with tandem duplication activation. Its greater efficacy, better tolerance (none of our patients had to discontinue treatment with dabrafenib due to AEs, unlike 3 patients with trametinib) and worse prognosis in PLGG with *BRAF V600E* mutant [10], may justify this hypothesis.

Previous reports and phase I/II clinical trials show that the AEs with these drugs are generally mild-moderate. Cutaneous

Table 2 BRAF V600E-mutated PLGG: patient characteristics, response, and toxicity with dabrafenib

Cases	Age at diagnosis (years); sex	Histologic diagnosis; tumor location	Prior surgery	Prior therapy	Age on treatment onset	Time on treatment (months)	Tumor response	Functional response	Side effects
Case 15	4,8; M	GG; spinal bulb—intramedullary	Biopsy	No	4.9 years	First round: 25 m; second round: 27 m (continue)	SD (first round); SD (second round)	Hemiparesis improved both times	Skin (grade II)
Case 16	4; F	PXA; temporal	GTR	No	4.9 years	First round: 10 m; second round: 24 m; third round: 14 m (continue)	CR (every time)	Stable	Skin (grade II)
Case 17	0.6; M	PA; hypothalamic-chiasmatic	Biopsy	VCR-CBCDA	1 year	13 m	SD*	Improved visual function	Skin (grade I)
Case 18	14.8; M	PA; mesencephalic-thalamic	Biopsy	VCR-CBCDA; BEV	17.6 years	20 m (continue)	CR	Improvement of ataxia and ocular movement	Skin (grade I) CPK increased (grade I)
Case 19	6,7; M	PA; hypothalamic-chiasmatic	Biopsy	VBL; BEV	7.5 years	18 m (continue)	SD	Stable	Skin (grade II)
Case 20	6,3; F	PA; optic pathway	Biopsy	VCR-CBCDA; BEV	8.4 years	16 m (continue)	PR	Improved visual function	Skin (grade II) Abdominal pain (grade I) Fatigue (grade II)
Case 21	17.8; M	PA; mesencephalic-thalamic	Biopsy	No	18 years	8 m (continue)	SD	Improved ocular movement	Skin (grade I)
Case 22	2.2; F	PA; optic pathway	Biopsy	VCR-CBCDA; VBL	7.1 years	6 m (continue)	SD	Stable	Skin (grade II) LDH increased (grade 1)
Case 23	6,2; F	GG; temporal and leptomeningeal dissemination	GTR	No	8.4 years	4 m (continue)	SD	Stable	Skin (grade I) AP increased (grade 1)

AP alkaline phosphatase, *ALT* alanine aminotransferase, *AST* aspartate aminotransferase, *BEV* bevacizumab, *CBCDA* carboplatin, *CPK* creatine phosphokinase, *CR* complete remission, *F* female, *GTR* grow total resection, *GG* ganglioglioma, *LDH* lactate dehydrogenase, *M* male, *PA* pilocytic astrocytoma, *PXA* pleomorphic xanthoastrocytoma, *PR* partial remission, *SD* stable disease, *VBL* vinblastine, *VCR* vincristine

*Case 17: In MRI, after 13 months with dabrafenib alone, a thickening and alteration of the signal in chiasma and optic nerves is identified. Therefore, it is decided to add trametinib to the treatment

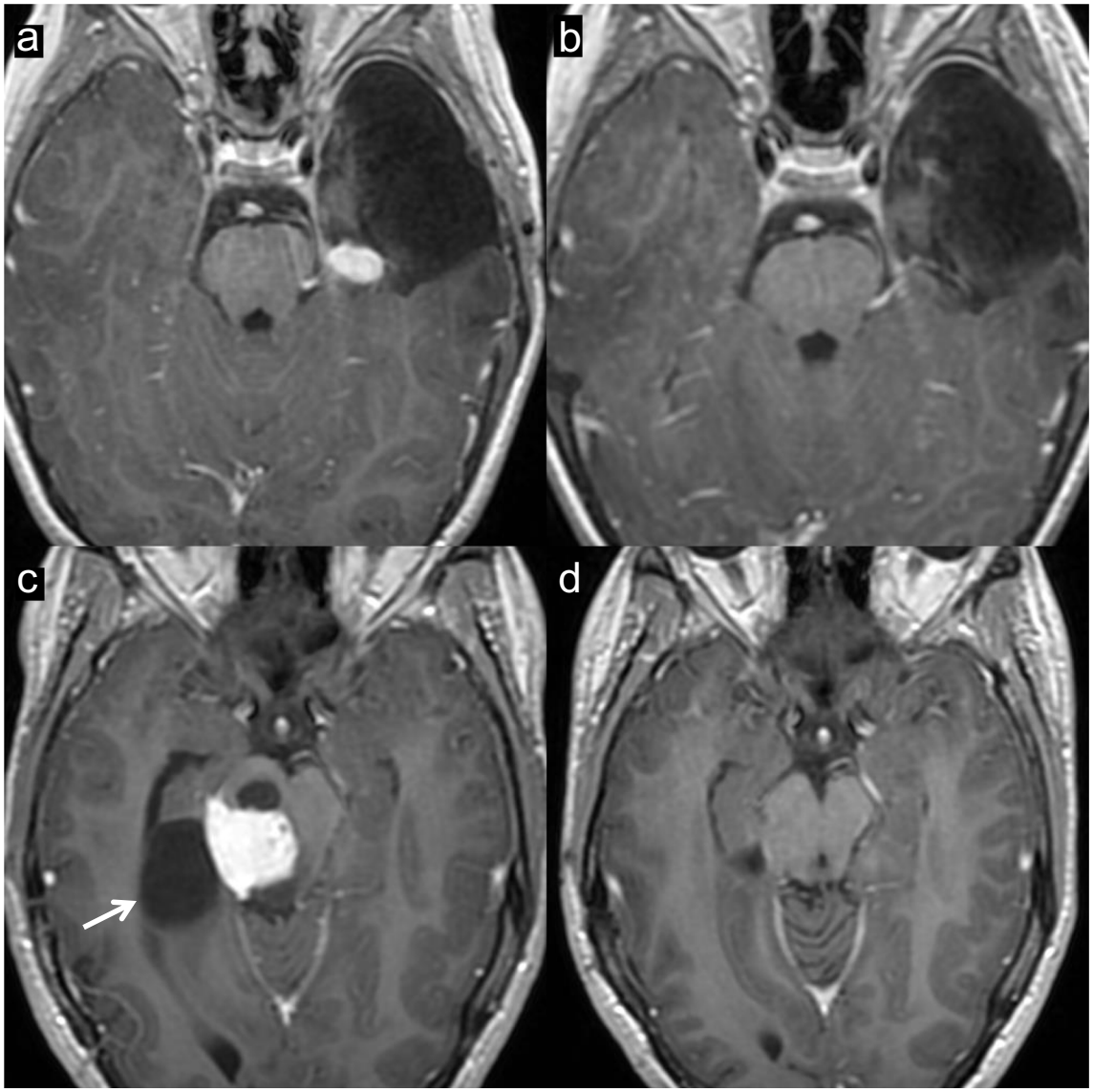

Fig. 2 MRI axial T1 + gadolinium in patient 1 pretreatment (**a**) and posttreatment (**b**) and in patient 2 (**c** pretreatment and **d** postreatment). There is a complete response in both patients. In patient 2 the lateral cystic component (**c**, white arrow) was surgically treated

AEs are the most common toxicity identified: various rashes, dermatitis acneiform, or paronychia with trametinib and hyperkeratosis, alopecia, palmar-plantar erythrodysesthesia, or papilloma with dabrafenib. Other AEs observed are fatigue, diarrhea, lymphedema, or nausea with trametinib and fatigue, pyrexia, arthralgia, headache, nausea, and vomiting with dabrafenib. Liver laboratory abnormalities and CPK elevation may occur with both drugs [20–25]. Cutaneous squamous cell carcinoma is an adverse event associated with dabrafenib, mostly seen in adults [23, 25, 26]. Other infrequent, but more serious, AEs includes cardiomyopathy, ocular alterations, pneumonitis, or rhabdomyolysis [20, 22, 24]. None of our patients had any serious toxicities. In fact, severe toxicity (cardiac, ocular) appears to have less impact on the pediatric population than in the adult [13, 14]. In our experience treatment was well-tolerated, with mostly mild, transient, and reversible grade I/II skin toxicity. Targeted therapy should be continued in the presence of mild skin toxicities and may require supportive care to improve symptoms, such as emollients, antihistamines, steroids (primarily topical), or short antibiotic courses. Occasionally, when there are intolerable ≥ grade 2 or 3 AEs, it is advisable, dose reduction, or treatment discontinuation. Treatment interruption for limited periods is unlikely to negatively influence disease control. Significantly, any disease growth can be reversed on restarting drug [22, 27]. For example, in case 10 we had to dose reduced, and despite not taking the theoretical recommended dose, therapy was efficacious. Importantly, these regimens are administered orally, being necessary fewer laboratory testing and hospital visits. Of note, all patients were able to perform normal daily activities.

Another unanswered question is whether combination therapy may be better than monotherapy, as suggested by the experience in melanoma [28], whereby associating MEK

and BRAF inhibitors there is a delay in the development of resistance to these therapies [21]. Combination reduces the skin toxicity, although is associated with an increase in other toxicities (i.e., anorexia or ocular toxicity) [27, 29]. Based on preclinical models, the inhibition of both BRAF/MEK also seems to be effective in PLGG with the *BRAF V600E* mutation of histological subtypes that have traditionally been resistant to chemotherapy treatment such as ganglioglioma or PXA [30]. Drobysheva et al. published a pediatric patient with disseminated PA with MAPK/ERK pathway activation that was treated with dabrafenib and trametinib with favorable clinical response [31]. There is an ongoing phase II clinical trial investigating the activity of dabrafenib in combination with trametinib in patients with PLGG and *BRAF V600* mutation, with the PLGG cohort treated with carboplatin plus vincristine as an active comparator (NCT02684058). Another uncertainty is whether combining targeted therapy and chemotherapy can be effective, which is being tested in in other diseases, such as Langerhans cell histiocytosis (NCT03585686).

Our findings add to the growing evidence that targeted therapies for PLGG both at progression and at diagnosis are effective in a high proportion of patients. Taking into account its efficacy, oral route, and toxicity profile, there is high enthusiasm in introducing them as first-line therapies for PLGG. Clinical trials aiming to clarify whether these drugs should replace upfront chemotherapy are ongoing or soon to open. Children's Oncology Group has a phase 3 randomized open-label clinical trial comparing selumetinib with standard chemotherapy (carboplatin and vincristine) in newly diagnosed or previously untreated PLGG (NCT04166409). International Society of Pediatric Oncology will be opening a similar trial in the coming months.

Conclusion

Our results confirm the good response observed in other reports to targeted therapy in patients with PLGG, with 100% of DCR in patients with dabrafenib and 78.6% with trametinib. Its effectiveness, oral route, and toxicity profile makes this therapeutic option optimal for being compared with traditional upfront chemotherapy. Ongoing prospective clinical trials will try to address this and other unknown relevant issues like functional response (i.e., visual improvement in optic pathway gliomas), optimal duration of therapy, and middle- and long-term AEs. Although we have some unanswered questions, it is clear that targeted therapy will gain more and more terrain in the therapeutic arena of PLGG.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00381-021-05138-3.

Declarations

Conflict of interest The authors have no conflicts of interest to declare that are relevant to the content of this article.

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