Salvage chemotherapy after failure of targeted therapy in a child with BRAF V600E low grade glioma

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Abstract

Targeted therapies are increasingly used in the management of pediatric low grade glioma. How-ever for patients who show resistance to these treatments, limited options are available. We pre-sent the case of a patient with BRAFV600 mutated low grade glioma who showed progression on a combination of trametinib and dabrafenib. Discontinuation of treatment was associated with a life-threatening deterioration and reintroduction of targeted therapy had no effect. The patient eventually showed a dramatic response to TPCV (thiguanine, procarbazine, CCNU and vincris-tine) , which suggests a role of chemotherapy in these situations.

Introduction

The last decades have witnessed a progressive paradigm shift in the non-surgical management of pediatric low-grade gliomas (PLGG). While radiation was historically the standard treatment, its use has progressively decreased with the development of chemotherapy strategies that have shown the possibility to delay or avoid radiotherapy in most patients[1]. A new shift is currently happening with evidence that alterations within the mitogen-activated protein kinase (MAPK) pathway affect most PLGGs and represent potential therapeutic targets[2]. Phase I and II trials have shown the efficacy of BRAF and MEK inhibitors in recurrent and/or refractory PLGG[34]. Response rates to these agents are promising and appear to be superior to those observed with chemotherapy, and clinical trials are ongoing to compare the efficacy of the new agents with standard chemotherapy in treatment naïve patients [5]. However, a number of questions remain unanswered regarding these new compounds, and in particular with regard to the management of patients who fail to respond or progress while treated with MEK or BRAF inhibitors. Herein we describe a patient with BRAFV600E mutated PLGG who progressed on a combination of dabrafenib and tramatenib. This patient eventually responded to a chemotherapeutic regimen consisting of thioguanine, procarbazine, lomustine and vincristine (TPCV) resulting in reversal of life-threatening symptoms.

Case description

A 2-year old male with a 1.5-year history of slight developmental delay and progressive visual disturbance associated nystagmus was referred for MRI by his ophthalmologist. Family history was potentially contributory due to consanguineous marriage. The child was showing marked nystagmus, and poor vision. No stigmata of neurofibromatosis type I (NF1) were present. MRI revealed a suprasellar mass, measuring 4.9cm x 5.6cm x 3.8cm extending to the hypothalamus, basal ganglia, thalami, posterior limb of internal capsules, optic tract and lateral geniculate nuclei, as well as the cerebral peduncles (Fig 1). The patient underwent a biopsy and histological examination was consistent with the diagnosis of PLGG with piloid features. Immunostains

showed positivity for GFAP and BRAFV600 mutation. Tumor cells were immunopositive for MLH1, MSH2, MSH6 and PMS2. The MIB-1 proliferation index was up to 2%. Further testing revealed the presence of a FGFR1 N546K mutation.

Postoperatively, the patient started weekly vinblastine for 70 weeks. He showed a mixed response to this treatment, with regression of the chiasmatic component, while the temporal component experienced mild progression. Due to the significant size of the tumor and poor vision, the child was then placed on dabrafenib. His tumor remained stable, although the vision continued to deteriorate. In this context, tramatenib was added 15 months later. No clear benefit of this addition was observed clinically and radiologically, and vision continued to progressively deteriorate to complete blindness. After two years of dual treatment, the patient presented with dysphagia, ataxia, dizziness, right-sided weakness and slurred speech and the decision was made switch to a trial of immune checkpoint inhibitor, as the tumor tested positive for PD-L1. One week after termination of the combination therapy, the patient experienced acute deterioration, with poor responsiveness, unsteady gait and worsening speech. His MRI showed substantial increase in tumor size. Re-introduction of dabrafenib did not improve his symptoms, and the GSC of the child was fluctuating between 7 and 11, despite high-doses of dexamethasone (4 mg//m2 QID). Parents declined the option of whole brain radiotherapy and it was decided to initiate TPCV. His condition remained severely compromised for 2 months. Due to severe side effects of high-dose dexamethasone, bevacizumab was initiated at 10mg/kg via IV biweekly for 4 cycles. His clinical condition started to improve after two cycles of TPCV, and after 4 cycles, the MRI scan show marked improvement (Fig 1). TPCV was continued for 6 cycles, after which it was discontinued due to thrombocytopenia. During treatment, he was offered intensive rehabilitation and was able to resume school 4 months following initiation of treatment. Two years after completion of TPCV, the patient is clinically well, with a Lansky score of 100% and stable MRI scan.

Discussion

PLGG encompass several entities characterized by different histopahtological features. During the last decade, molecular characterization of PLGG has identified a number of recurrent alterations, with the majority involving the MAPK pathway[6]. In children without NF1, the most common alterations in this pathway include the*KIAA1549-BRAF* fusion and the BRAFV600E mutation[7]. Both alterations can be targeted, and the use of MEK inhibitors in patients with PLGG harboring BRAF fusion or BRAF inhibitors in patients with PLGG harboring BRAFV600E mutation have shown promising response rate[43].

Although PLGGs associated with BRAF mutation appear to have a more aggressive behavior [8], they show an excellent response to BRAF inhibitors. Hargrave et al conducted a trial of dabrafenib in children with BRAF mutated PLGG and reported a partial response in 19 of 27 evaluable patients, and a 1-year event free survival of 85%[3]. More recently, Nobre et al compared 2 cohorts of patients with BRAF mutated PLGG treated with chemotherapy or BRAF inhibitors (vemurafenib or dabrafenib) and demonstrated a clear advantage for targeted treatments, with an overall objective response rate of 28% and 71%, respectively[5]. Report on the combination of BRAF and MEK inhibitors in BRAF mutated LGG are pending. The rationale for this combination is based on superior outcome observed in patients with BRAF mutated melanomas randomized to either dabrafenib or dabrafenib and trametinib[9].

However, the risk of developing resistance to BRAF inhibition exists and has been well documented in melanoma. In PLGG, there has been limited focus on this issue and the management of patients who show progression during treatment with BRAF inhibitors remains challenging. Mulcahy Levy et al recently described a patient with BRAFV600E mutated ganglioglioma who developed resistance to vemurafenib. The addition of chloroquine to vemurafenib was associated with durable clinical improvement as well radiographic response[10]. A clinical trial is ongoing to confirm these early data.

As the response rate of BRAFV600E PLGG is extremely high for BRAF inhibition, the fact that our patient had limited benefit of BRAF inhibition is intriguing. A plausible mechanism can be the additional FGFR1 N546K mutation. In contrast to FGFR gene fusions, point mutations in FGFR1 tend to be associated with other RAS/MAPK mutations and are showing less favorable outcome[7].

Interestingly, the acute clinical deterioration of our patient within a week of discontinuation of the BRAF/MEK inhibition is not uncommon in BRAFV600E tumors. This precluded his inclusion in any clinical trial. Re-challenging with dabrafenib did not show any evidence of efficacy and the decision was made to proceed with chemotherapy, using the TPCV regimen. This regimen has been compared to the combination of vincristine and carboplatin in a randomized trial and has shown better event free survival at 5 years[11]. However, this trial did not include any molecular study and whether chemotherapy regimens have a better activity in specific molecular subgroups is unknown.

Our experience is intriguing and provides some evidence that salvage chemotherapy is still an option when targeted therapy fail. As most BRAFV600E PLGG recur rapidly after cessation of targeted therapies, the sustained tumor control, 2 years after completion of chemotherapy is encouraging, suggesting a different and potentially synergistic role for chemotherapy is such situations. Further studies will determine whether a combination of targeted and chemotherapy regimens are superior to each of these as a single modality.

Disclosures:

Eric Bouffet is a member of an advisory board of Novartis. Other authors do not report any conflict of interest.

Figure 1:

MRI scan (FLAIR Sequence) at the time of diagnosis (A); at the time of progression, before starting TPCV (B); 6 months after initiation of TPCV (C); 18 months after completion of TPCV (D)

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