Received: 5 June 2020 | Accepted: 21 June 2020

DOI: 10.1002/pbc.28561

Pediatric Blood & Cancer

SIOP INTERNATIONAL SOCIETY OF PAEDIATRIC ONCOLOGY

aspho The American Society of Pediatric Hematology/Oncology

WILEY

LETTER TO THE EDITOR

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

To the Editor:

A shift is happening in the nonsurgical management of pediatric low-grade glioma (PLGG), with evidence that alterations within the mitogen-activated protein kinase (MAPK) pathway affect most PLGGs and represent potential therapeutic targets.[1] Early trials have shown efficacy of BRAF and MEK inhibitors in recurrent/refractory PLGG.[2,3] Response rates are promising and appear to be superior to those observed with chemotherapy.[4] However, little is known regarding the management of patients who fail to respond or progress while treated with MEK or BRAF inhibitors. We describe a patient with BRAF V600E mutated PLGG who progressed on a combination of dabrafenib and tramatenib, and eventually responded to thioguanine, procarbazine, lomustine, and vincristine (TPCV) resulting in reversal of life-threatening symptoms.

A 2-year-old male was referred for magnetic resonance imaging (MRI) by his ophthalmologist for nystagmus and poor vision. MRI revealed a suprasellar mass, measuring 4.9 × 5.6 × 3.8 cm extending to the hypothalamus and the posterior optic tracts (Figure 1). Tumor biopsy was consistent with the diagnosis of PLGG with piloid features. Immunostains showed positivity for GFAP and BRAF V600 mutation. Further testing revealed the presence of a FGFR1 N546K mutation.

Postoperatively, the patient started weekly vinblastine for 70 weeks with stable disease. 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. However, his vision continued to progressively deteriorate to complete blindness. After 2 years of dual treatment, the patient presented with evidence of neurological deterioration and the decision was made to switch to a trial of immune checkpoint inhibitor, as the tumor tested positive for PD-L1. One week after discontinuation of the combination, the patient experienced acute neurological deterioration. MRI showed substantial increase in tumor size. Reintroduction of dabrafenib did not improve symptoms, and the Glascow Coma Scale of the child was fluctuating between 7 and 11, despite high doses of dexamethasone. Parents declined 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 biweekly for four cycles. His clinical condition started to improve after two cycles of TPCV, and after four cycles, the MRI scan showed marked improvement (Figure 1). TPCV was continued for six cycles, after which it was discontinued due to thrombocytopenia. Two years after completion of TPCV, the patient is clinically well, with a Lansky score of 100% and stable MRI scan.

During the last decade, molecular characterization of PLGG has identified a number of recurrent alterations, with the majority involving the MAPK pathway,[5] the most common including the *KIAA1549-BRAF* fusion and the BRAF V600E mutation.[6] Although PLGGs associated with BRAF mutation appear to have a more aggressive behavior,[7] they show an excellent response to BRAF inhibitors. A trial of dabrafenib in children with BRAF mutated PLGG reported a partial response in 19/27 evaluable patients, and a 1-year event-free survival of 85%.[2] More recently, Nobre et al compared two cohorts of patients with BRAF mutated PLGG treated with chemotherapy or BRAF inhibitors and demonstrated a clear advantage for targeted treatments.[4]

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 BRAF V600E mutated ganglioglioma who developed resistance to vemurafenib. The addition of chloroquine to vemurafenib was associated with durable clinical improvement as well radiographic response.[8] A clinical trial is ongoing to confirm these early data.

As the response rate of BRAF V600E 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.[6]

Interestingly, the acute clinical deterioration of our patient within a week of discontinuation of the BRAF/MEK inhibition is not uncommon in BRAF V600E tumors. This precluded his inclusion in any clinical trial. Rechallenging 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.[9] However, this trial did not include any molecular study, and whether chemotherapy regimens have a better activity in specific molecular subgroups is unknown.

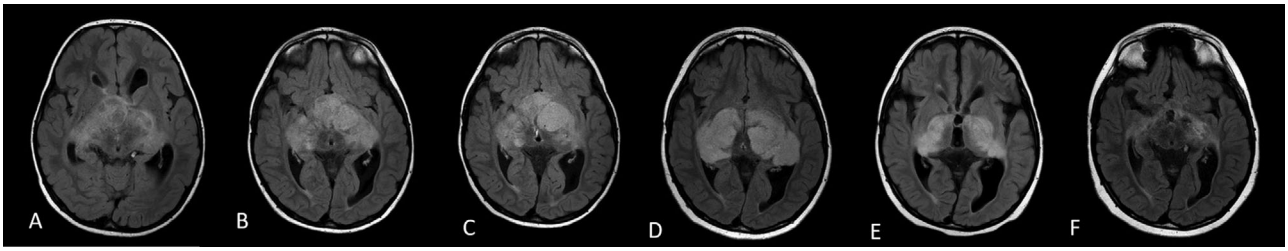

FIGURE 1 Magnetic resonance imaging (MRI) scan (FLAIR sequence) at the time of diagnosis (A); at completion of 70 weeks of vinblastine (B); 3 months later, before starting dabrafenib (C); at the time of progression, before starting thioguanine, procarbazine, lomustine, and vincristine (TPCV) (D); 6 months after initiation of TPCV (E); 18 months after completion of TPCV (F)

Our experience is intriguing and provides some evidence that salvage chemotherapy is still an option when targeted therapy fails. As most BRAF V600E PLGG recur rapidly after cessation of targeted therapies,[3,4] the sustained tumor control 2 years after completion of chemotherapy is encouraging, suggesting a different and potentially synergistic role for chemotherapy in such situations. Further studies will determine whether a combination of targeted and chemotherapy regimens are superior to each of these as a single modality.

CONFLICT OF INTEREST

Eric Bouffet is a member of an advisory board of Novartis. The other authors declare that there is no conflict of interest.

Musthafa Raswoli[1]
Liana Nobre[1]
Cynthia Hawkins[2]
Ute Katharina Bartels[1]
Uri Tabori[1]
Eric Bouffet[1]

[1] *Division of Haematology/Oncology, The Hospital for Sick ChildrenUniversity of Toronto, Toronto, Ontario, Canada*
[2] *Department of Laboratory Medicine and Pathobiology, The Hospital for Sick ChildrenUniversity of Toronto, Toronto, Ontario, Canada*

Correspondence
Eric Bouffet, Division of Haematology/Oncology, The Hospital for Sick Children, University of Toronto, 555 University Ave, Toronto, ON M5G 1X8, Canada.
Email: eric.bouffet@sickkids.ca

ORCID

Eric Bouffet https://orcid.org/0000-0002-6832-6539

REFERENCES

1. Packer RJ, Pfister S, Bouffet E, et al. Pediatric low-grade gliomas: implications of the biologic era. *Neuro Oncol*. 2017;19(6):750-761.
2. Hargrave DR, Bouffet E, Tabori U, et al. Efficacy and safety of dabrafenib in pediatric patients with BRAF V600 mutation-positive relapsed or refractory low-grade glioma: results from a phase I/IIa study. *Clin Cancer Res*. 2019;25(24):7303-7311.
3. Fangusaro J, Onar-Thomas A, Young Poussaint T, et al. Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicentre, phase 2 trial. *Lancet Oncol*. 2019;20(7):1011-1022.
4. Nobre L, Zapotocy M, Ramaswamy V, et al. Outcomes of BRAF V600E pediatric gliomas treated with targeted BRAF inhibition. *JCO Precis Oncol*. 2020;4:561-571.
5. Zhang J, Wu G, Miller CP, et al. Whole-genome sequencing identifies genetic alterations in pediatric low-grade gliomas. *Nat Genet*. 2013;45(6):602-612.
6. Ryall S, Zapotocky M, Fukuoka K, et al. Integrated molecular and clinical analysis of 1,000 pediatric low-grade gliomas. *Cancer Cell*. 2020;37(4):569-583.e5.
7. Lassaletta A, Zapotocky M, Mistry M, et al. Therapeutic and prognostic implications of BRAF V600E in pediatric low-grade gliomas. *J Clin Oncol*. 2017;35(25):2934-2941.
8. Mulcahy Levy JM, Zahedi S, Griesinger AM, et al. Autophagy inhibition overcomes multiple mechanisms of resistance to BRAF inhibition in brain tumors. *Elife*. 2017;6:e19671.
9. Ater JL, Zhou T, Holmes E, et al. Randomized study of two chemotherapy regimens for treatment of low-grade glioma in young children: a report from the Children's Oncology Group. *J Clin Oncol*. 2012;30(21):2641-2647.