Neuro-Oncology
23(10), 1627–1628, 2021 | https://doi.org/10.1093/neuonc/noab164 | Advance Access date 12 July 2021

Selumetinib for optic pathway glioma: Seeing through the fog, (not yet) the end of the tunnel?

Vijay Ramaswamy and Ute Bartels

Division of Haematology/Oncology, The Hospital for Sick Children, Toronto, Ontario, Canada (V.R., U.B.)

Corresponding Author: Ute Bartels, Division of Hematology/Oncology, Pediatric Brain Tumor Program, The Hospital for Sick Children, 555 University Avenue, Toronto, ON M5G 1X8, Canada (ute.bartels@sickkids.ca).

See the article by Fangusaro et al. pp. 1777–1788

Low-grade gliomas in children whenever not amenable to a resection represent one of the most challenging entities in pediatric neuro-oncology.[1] Although transformation to higher-grade tumors is rare, current therapies consist of multiple rounds of conventional chemotherapy with a goal to preserve function, in anticipation of potential senescence where many children still proceed to radiotherapy. Unfortunately, many children suffer from lifelong sequelae of their tumor or treatment, and as such new treatment approaches are being explored.[2] A major biological distinction between adult and pediatric low-grade gliomas (pLGG) is a near-uniform enrichment for activating lesions in BRAF (either fusion or mutation) with subsequent activation of the Ras/MAPK pathway, where MEK inhibition has been suggested as a rationale therapy.[1] First results on selumetinib for recurrent/refractory pLGG from the Pediatric Brain Tumor Consortium (PBTC) have shown very promising activity.[3,4] This has sparked an immense interest in pursuing MEK inhibition as a first-line therapy for pLGG, in the form of a randomized study from the Children's Oncology Group (COG) comparing 1 year of carboplatin/vincristine to 2 years of selumetinib monotherapy (NCT04166409).

The PBTC-029 is a multi-strata phase I/II study and outcomes from stratum 1 (pilocytic astrocytoma) and stratum 3 (NF1-associated pLGG) have been previously published.[3,4] Fangusaro et al report the results of stratum 4 of the trial which enrolled all non–NF1-associated recurrent and progressive optic pathway gliomas (OPG).[5] In a cohort of 25 pretreated recurrent OPG, 24% of patients had a partial response defined as a 50% reduction in 2-dimensional volume, and a further 50% of patients had stable disease with responses varying from 0% to 50%, and 25% of the cohort progressed on treatment. The progression-free survival was also encouraging compared to historical studies with significantly improved response rates compared to PBTC-022 as well as single-agent vinblastine. Functional outcomes were included, with 4 of the 19 evaluable patients having improvement in visual acuity and 5 of the 19 showing improvement in visual fields.

The introduction of MEK inhibition as a treatment option for pediatric OPG is a huge leap forward in providing neuro-oncologists with a powerful new armamentarium. The current study combined with the initial report of PBTC-029 has shown significant cytoreduction of relapsed pLGG in a manner not seen previously with conventional chemotherapy. The initial results of PBTC-029 have prompted many clinicians to consider MEK inhibition in patients with visual loss, either upfront or at first recurrence after chemotherapy. Pediatric neuro-oncologists have been using trametinib off-label in MAPK-activated pLGG, which is approved for adult malignancies and for which a liquid formulation is available, or more recently selumetinib off-label which has been approved for NF1-associated plexiform neurofibromas.

However, despite these exciting and encouraging results, several major questions remain unanswered, which should raise concerns around introducing MEK inhibition into routine use, particularly at diagnosis. Indeed, the results of this study, although promising, raise additional questions specifically with respect to duration of therapy, selection of patients, acute and long-term side effects, quality of life, and evaluation of functional outcomes. Additional insights from an ongoing pan-Canadian study of trametinib in recurrent pLGG and the open upfront randomized study from the COG comparing selumetinib to carboplatin/vincristine (ACNS1831/1833) may help resolve some of these open questions (NCT04166409/NCT03871257).[6]

A major limitation of PBTC-029 is the lack of mandatory tissue sampling, where only 6 of the 25 patients had tissue available for screening of either the KIAA1549-BRAF fusion or BRAF V600E point mutation. Although this is likely due to a paucity of biopsy of OPG prior to the molecular era, it does render the interpretation of this study difficult. Previous work has suggested that BRAF V600E-mutant tumors are more aggressive than BRAF-fused and as such it is difficult to discern from this study if responses are equally durable between both of these groups.[7,8] The progression-free survival is encouraging, particularly the relative stability after discontinuation of therapy in this heavily pretreated cohort. However, the stability observed after 24 months in this cohort is in contrast to the initial PBTC-029 report: in stratum 1, all BRAF mutant tumor and over 50% of BRAF-fused tumors progressed, early after discontinuation of therapy. Stratum 1 was comprised

of 40% hypothalamic and optic pathway tumors, and as such suggests that there is a difference between these 2 cohorts, possibly related to an enthusiasm to enroll patients earlier within this expansion cohort, or potentially those enrolled based on more subjective interpretations of progression.

Visual outcomes were limited but suggested 20% of patients had improved in acuity and/or visual fields which is comparable to PBTC-022 which employed bevacizumab and irinotecan.[9] Comparison to previous studies is challenging as visual outcomes have been poorly collected in trials of conventional chemotherapy.[10,11] Indeed, it raises the question whether radiological response and progression-free survival are the appropriate primary outcomes to assess in pLGG. Moving forward, consideration should be given to trial designs where functional outcomes are set as the primary objective. The current randomized COG study does mandate teller acuity card assessment and will hopefully clarify the role of MEK inhibition in reversing visual loss.

Clinical trials should continue to be pursued that build upon these data, where tissue is mandatory and can be adequately correlated with the underlying molecular alteration. This study while incredibly promising, should raise some doubts around incorporating a new standard of care outside a clinical trial. The apparent discrepancy in the durability of responses between stratum 1 and 4 would suggest that continued investigation under the oversight of controlled clinical trials with central molecular and radiological review is still required. Moreover, the natural history of pLGG suggests eventual senescence, and as such the natural history after MEK inhibitor therapy requires careful investigation. Nonetheless, the emergence of targeted agents in pLGG raises the specter of significantly improved outcomes for this incredibly challenging condition and provides hope that with continued investigation and combinatorial therapy, we can significantly improve functional outcomes of children with low-grade gliomas.

Acknowledgments

The text is the sole product of the authors and no third party had input or gave support to its writing.

References

1. Jones DTW, Kieran MW, Bouffet E, et al. Pediatric low-grade gliomas: next biologically driven steps. *Neuro Oncol.* 2018;20(2):160–173.
2. Krishnatry R, Zhukova N, Guerreiro Stucklin AS, et al. Clinical and treatment factors determining long-term outcomes for adult survivors of childhood low-grade glioma: a population-based study. *Cancer.* 2016;122(8):1261–1269.
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. Banerjee A, Jakacki RI, Onar-Thomas A, et al. A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor Consortium (PBTC) study. *Neuro Oncol.* 2017;19(8):1135–1144.
5. Fangusaro J, Onar-Thomas A, Poussaint TY, et al. A phase 2 trial of selumetinib in children with recurrent optic pathway and hypothalamic low-grade glioma without NF1: a pediatric brain tumor consortium study. *Neuro Oncol.* 2021;23(10):1777–1788.
6. Perreault S, Larouche V, Tabori U, et al. A phase 2 study of trametinib for patients with pediatric glioma or plexiform neurofibroma with refractory tumor and activation of the MAPK/ERK pathway: TRAM-01. *BMC Cancer.* 2019;19(1):1250.
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. 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.
9. Gururangan S, Fangusaro J, Poussaint TY, et al. Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas – a Pediatric Brain Tumor Consortium study. *Neuro Oncol.* 2014;16(2):310–317.
10. Lassaletta A, Scheinemann K, Zelcer SM, et al. Phase II weekly vinblastine for chemotherapy-naïve children with progressive low-grade glioma: a Canadian Pediatric Brain Tumor Consortium study. *J Clin Oncol.* 2016;34(29):3537–3543.
11. 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.