Recurrent ganglioglioma in adults treated with BRAF inhibitors

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Practice points

- A small subset of adult gliomas with clinically actionable mutations may be targets for currently available small molecule inhibitors approved for other cancer indications.
- Gangliogliomas, uncommon adult gliomas (seen in <1% of adult series), in approximately 40% manifest the BRAF V600E mutation and which is targetable by BRAF (and MEK) inhibitors.
- BRAF mutations in gliomas can be determined by a commercially available analytic that is commonly used in evaluating metastatic melanoma.
- Several commercially available agents (vemurafenib, dabrafenib and trametinib) used in the treatment of metastatic melanoma may be repurposed for the treatment of gliomas with BRAF V600E mutations.
- This small case series and another in pediatrics suggest that recurrent gangliogliomas with BRAF V600E mutations may respond to targeted therapy with BRAF inhibitors.
- An ongoing cooperative group study in pediatrics is exploring the utility BRAF inhibitors in pediatric gliomas with actionable mutations in BRAF.

Thirteen adult patients with temozolomide, surgery and radiation refractory ganglioglioma were screened for the *BRAF* V600E mutation. Three (23%) were found positive for the presence of the *BRAF* mutation and were treated with the *BRAF* inhibitor dabrafenib. Dabrafenib was well tolerated with no grade 3 or higher toxicity. The median number of cycles was 7 (a cycle was defined as 1 month of daily dabrafenib) and best response was stable disease in two patients and a partial response in one patient. Median progression-free survival was 7 months with a range of 4–10 months.

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Oncologists increasingly utilize targeted therapy as a novel treatment modality in cancers with well-characterized druggable molecular abnormalities. The ability to target driver mutations in cancer has in some instances obviated the need for use of cytotoxic chemotherapy. Notwithstanding more than 100 available targeted therapies in oncology, currently the use of

targeted therapy for the treatment of glioma in the USA is limited to two indications; the oral mTOR inhibitor everolimus for the treatment of subependymal giant cell astrocytoma occurring in a subset of patients and primarily children with tuberous sclerosis and the VEGF ligand-binding monoclonal antibody bevacizumab for recurrent glioblastoma in adults.

KEYWORDS

- BRAF inhibitors
- BRAF V600E mutation
- dabrafenib
- ganglioglioma

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Table 1. Patient characteristics and treatment.													
Patient	Gender/age (y)	Histology/tumor location	Initial therapy		First salvage therapy			Second salvage therapy			Dabrafenib Salvage therapy		
			Surgery	Radiotherapy	Surgery	Radiotherapy	Chemotherapy (cycles)	Surgery	Radiotherapy	Chemotherapy (cycles)	Response	PFS (months)	OS (months)
1	F/26	Gr1/frontal	STR	54 Gy	–	–	TMZ (6)	–	–	–	SD	4	6
2	M/34	Gr1/frontal	GTR	–	STR	54 Gy	–	–	–	TMZ (4)	SD	7	12
3	M/45	Gr1/temporal	GTR	–	–	54 Gy	–	–	–	TMZ (3)	PR	10	16
Female; GTR: Gross total resection; M: Male; OS: Overall survival from onset of dabrafenib; PFS: Progression-free survival; PR: Partial response; SD: Stable disease; STR: Subtotal resection; TMZ: Temozolomide.													

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The molecular characterization of gliomas continues to evolve and has become commonplace in clinical practice both for diagnostic purposes, for example, the presence of the 1p19q codeletion, a signature of tumors of oligodendroglial lineage as well as by providing prognostic information, for example, the presence of *IDH1* mutation in WHO grade II and III gliomas. Additionally, the 1p19q codeletion in oligodendroglial tumors and methylation of the promoter of the DNA repair gene, *MGMT* (methylguanine methyltransferase), are predictive biomarkers that impact allocation of treatment and outcome.

Recently, a mutation in the *BRAF* oncogene, BRAF V600E, has been characterized as commonly present in melanoma as well as a variety of WHO Grade I gliomas including gangliogliomas wherein the mutation is present in approximately 30% [1–4]. Gangliogliomas constitute 1% of all primary brain tumors and the majority (>90%) pathologically are defined as WHO Grade I [5]. Gangliogliomas are found most often in children, in the frontal and temporal lobes, are the most common tumor associated with chronic temporal lobe epilepsy and optimal therapy and best survival is seen following complete surgical resection. The role for adjuvant radiotherapy is uncertain as is the efficacy of chemotherapy. The presence of the BRAF V600E mutation in gangliogliomas suggests the possibility that use of small molecule *BRAF* inhibitors may have efficacy in the recurrent setting. A single case report of treating three children with recurrent ganglioglioma and *BRAF* inhibitors has been reported [6,7]. To date however there are no reports of treating adults with recurrent ganglioglioma and BRAF inhibitors.

Methods & patient characteristics

Thirteen gangliogliomas in adult patients were screened by real-time polymerase-chain reaction assay (Cobas 4800 *BRAF* V600 Mutation test, Roche Molecular Systems) for the presence of the V600E mutation, among which 3 (23%) were positive. Three patients with recurrent ganglioglioma and positive for the V600E mutation were treated with dabrafenib, a second-generation *BRAF* inhibitor, following disease progression after previous therapy that included surgery, radiotherapy and temozolomide chemotherapy (Table 1).

Following ascertainment of the BRAF mutation, each patient was offered dabrafenib as an off-label treatment. Coverage of dabrafenib was borne by the patients' medical insurer. Consent for treatment was obtained before initiating treatment after

disclosure of alternative therapy, limited experience with dabrafenib in this context and potential toxicity of therapy based on published data seen when used for metastatic melanoma. Dabrafenib was administered orally at a dose of 150 mg twice per day. Patients were seen and examined monthly that as well included a complete blood count and comprehensive chemistry panel. Repeat contrast brain MRI was performed every 2 months or more often if clinically indicated [8].

Results

Dabrafenib was well tolerated and there were no CTC grade 3 or higher toxicities. The median number of cycles (defined as 1 month of dabrafenib) was 7 with a range of 4–10. Best radiographic response following two cycles of dabrafenib was stable disease in two patients and partial response in one patient. Two patients following progression on dabrafenib elected another salvage therapy and one patient proceeded to hospice. Median progression-free survival was 7 months (range 4–10 months). Median overall survival from onset of dabrafenib was 12 months (range 6–16 months).

Discussion

A small case series of adult patients such as the current report is hypothesis generating only but suggests inhibition of *BRAF* in gangliogliomas with V600E mutations may, if confirmed in a larger and prospective trial, constitute a novel treatment paradigm. More recently and in metastatic melanoma

the combined use of both a *BRAF* (dabrafenib) and *MEK* inhibitor (trametinib) has proved more effective than single agent *BRAF* inhibition targeted therapy and may overcome resistance to single agent *BRAF*-directed therapy [9]. Whether this combination of vertical signal pathway inhibition is more active in V600E-mutant gliomas such as ganglioglioma is uncertain but warrants further investigation. The rarity of V600E-mutant gliomas in adults (as for example in pleomorphic xanthoastrocytomas, gangliogliomas and pilocytic astrocytomas) likely will require a cooperative group effort so as to insure sufficient accrual and statistical validation of BRAF inhibitors as an alternative treatment in these uncommon gliomas. A pediatric cooperative group study (NCI-2012-03173, NCI-2014-00387 and NCI-2014-01467) is currently investigating the utility of BRAF and MEK inhibitors in children with V600E-mutated recurrent primary brain tumors and likely will further inform as to the utility of this approach in patients with recurrent gliomas and BRAF mutations.

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