Rapid Clinical and Radiographic Response With Combined Dabrafenib and Trametinib in Adults With *BRAF*-Mutated High-Grade Glioma

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Abstract

BRAF V600E mutations have been successfully treated with targeted therapy in melanoma, non-small cell lung cancer, and thyroid cancer. Interestingly, these mutations have also been identified in a subset of pediatric and adult brain tumors, with several cases reportedly responding to targeted therapy. However, these reports have been limited to single-agent *BRAF* inhibitor therapy and recurrent disease. Herein, we report dramatic clinical and radiographic responses to combination dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) in 2 adults with high-grade gliomas (HGGs), with 1 patient treated in the first-line setting. These observations, together with prior case reports, advocate for routine screening of *BRAF* point mutations in adult HGGs, and suggest that treatment with dual-targeted therapy, even in newly diagnosed cases, is safe and effective.

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The activating *BRAF* V600E mutation has been successfully targeted with dual molecular therapy in melanoma, non-small cell lung carcinoma (NSCLC), and thyroid cancer. *BRAF* V600E mutations have also been identified in a subset of patients with pediatric and adult brain tumors, and several case reports have indicated the potential efficacy of targeted therapy in these patients. To date, these studies have mostly been performed using single-agent *BRAF* inhibitor therapy in recurrent low-grade gliomas (LGGs; Table 1). This report describes the use of combination dabrafenib (*BRAF* inhibitor) and trametinib (MEK inhibitor) in 2 adults with high-grade gliomas (HGGs). The first patient was treated at time of

diagnosis, whereas the second was treated at time of recurrence in conjunction with the antiangiogenic agent bevacizumab. Both patients showed rapid and dramatic clinical and radiographic responses.

Case Reports

Patient 1

Patient 1 was a previously healthy 28-year-old female who developed generalized tonic-clonic seizures and was ultimately found to have a left hippocampal lesion. The seizures initially began when the patient was 5 weeks pregnant; however, a noncontrast head CT at the time was unremarkable. A postpartum brain T2-weighted,

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Table 1. Studies Using Single-Agent BRAF Inhibitors in Recurrent Low-Grade Gliomas

Age/Sex	Diagnosis	BRAF Inhibitor	Response	Duration of Response	Reference
Pediatric					
2 mo, F	Hypothalamic-chiasmatic glioma	Dabrafenib	PR	>10 mo ^a	40
18 mo, F	Peduncular anaplastic ganglioglioma	Vemurafenib	PR	>20 mo ^a	33
23 mo, M	Pilomyxoid astrocytoma	Vemurafenib	PR	>15 mo ^a	36
28 mo, M	Brainstem ganglioglioma	Vemurafenib	PR	>6 mo ^a	39
6 y, M	Thalamic anaplastic ganglioglioma	Vemurafenib	PR	3 mo	33
8 y, M	Brainstem ganglioglioma	Vemurafenib	PR	>14 mo ^a	38
9 y, M	Glioblastoma	Vemurafenib	CR	>6 mo ^a	16
13 y, F	Brainstem ganglioglioma	Vemurafenib	PR	>12 wk ^a	34
Adult					
25 y, M	Anaplastic ganglioglioma	Dabrafenib	CR	>24 mo ^a	41
34 y, F	PXA	Vemurafenib	SD	4 mo	28
35 y, F	Anaplastic PXA	Dabrafenib	PR	3 mo	35
41 y, M	Anaplastic PXA	Vemurafenib	CR	>12 wk ^a	42
43 y, M	Anaplastic PXA	Vemurafenib	PD	NR	28
47 y, F	PXA	Vemurafenib	SD	6 mo	28
53 y, M	PXA	Vemurafenib	PR	10 mo	28

Abbreviations: CR, complete response; F, female; M, male; NR, not reported; PD, progressive disease; PR, partial response; PXA, pleomorphic xanthoastrocytoma; SD, stable disease.

^aDuration of response at time of publication.

fluid-attenuated inversion recovery (T2/FLAIR) MRI performed 9 months later revealed an ill-defined hyperintense lesion with central contrast enhancement within the left hippocampal body extending into the hippocampal tail, considered to be most consistent with a LGG. A repeat MRI 3 months later demonstrated an increase in size of the lesion with local extension into the basal ganglia, anterior temporal lobe, and midbrain. Given the rate of progression, a left temporal craniotomy was performed, with a subtotal resection achieved. The postoperative course was complicated by right-sided hemiparesis and word-finding difficulties due to a subdural hematoma requiring evacuation and obstructive hydrocephalus requiring shunt placement.

Histopathologic evaluation of the resected tumor showed a diffusely infiltrative glioma with moderate to dense cellularity, marked pleomorphism, brisk mitotic activity, and predominantly epithelioid morphology (Figure 1A). Although necrosis was not convincingly present, large areas of hemorrhage, focal endothelial hyperplasia (Figure 1B) and vascular thrombosis were present. The tumor was widely infiltrative (Figure 1C). Fluorescence in situ hybridization (FISH) showed polysomy of chromosome 7 al-

beit without *EGFR* amplification, and there was no *PTEN* (or monosomy 10q) loss. A targeted gene sequencing panel (FoundationOne, Foundation Medicine, Cambridge, MA) revealed loss of *CDKN2A/B* and *TERT* promoter mutations. Interestingly, gene sequencing also revealed the presence of a *BRAF* V600E mutation, which was corroborated by immunohistochemistry (Figure 1D). No mutations in *IDH1* or *IDH2* were identified through sequencing, and immunohistochemistry showed retained *ATRX* and *INI1* expression. *MGMT* was unmethylated. Brisk proliferation was evident on Ki-67, particularly in the epithelioid regions. No areas reminiscent of classic pleomorphic xanthoastrocytoma (PXA) were identified in this tumor. Specifically, there was lack of eosinophilic granular bodies and reticulin-rich areas.

The collective findings of diffuse growth pattern, largely epithelioid histology, marked anaplasia, and lack of classic PXA phenotype, in conjunction with polysomy of chromosome 7 and *TERT* promoter mutations, were favored to represent epithelioid glioblastoma (GBM).

A brain MRI performed 4 weeks postoperatively demonstrated interval increased involvement of

Figure 1. Histopathology of tumor from patient 1, composed of mostly epithelioid glial cells (A; hematoxylin-eosin [HE] staining, original magnification x20) with focal endothelial hyperplasia (B, asterisk; HE staining, original magnification x20), prominent infiltrative growth pattern (C; HE staining, original magnification x10), and diffuse cytoplasmic immunoreactivity for mutant *BRAF* V600E (D; original magnification x20).

the anterior left temporal lobe and thalamus (Figure 2A, black arrow), with residual disease enhancement extending from the resection cavity into the cerebral peduncle inferiorly, as well as interval development of enhancement of cranial nerves V, VII, and VIII, along with the optic chiasm and pituitary stalk, and new nodular foci of enhancement along the temporal dura (Figure 2A, white arrow). Overall, these findings were consistent with leptomeningeal gliomatosis. Despite the concern for continued progression in the absence of aggressive therapy, all adjuvant treatment was deferred due to persistent

Figure 2. Brain MRI of patient 1 before (A) and 4 weeks after (B) treatment with dabrafenib and trametinib. Images are representative coronal views from the postcontrast T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences, which demonstrate contrast-enhancing lesions in the thalamic region (black arrow) and temporal dura (white arrow), consistent with residual disease postresection and new metastatic foci of disease, respectively.

poor functional status. Unfortunately, 4 months after surgery the patient continued to have persistent poor functional status, precluding the possibility of even radiation monotherapy, so the decision was made to begin dabrafenib (150 mg, twice daily) and trametinib (2 mg, once daily). Remarkably, within 1 week of initiating dual-targeted therapy, the patient experienced a dramatic improvement in speech, overall strength, and endurance, although she continued to have right-sided hemiparesis. Four weeks later, repeat brain MRI revealed near complete resolution of the leptomeningeal gliomatosis with no evidence of intraparenchymal disease progression, although there was a persistent T2/FLAIR signal surrounding the resection cavity (Figure 2B). Over the subsequent months, the patient experienced gradual improvement in right-sided hemiparesis while experiencing no significant side effects from the combination therapy.

Unfortunately, 11 months after initiating treatment, MRI showed disease progression in the form of leptomeningeal enhancement along the cerebellum, although the residual tumor enhancement in the left temporal lobe remained unchanged. Therefore, dabrafenib and trametinib were discontinued.

Patient 2

Patient 2 was a 24-year-old male with a known left posterior frontal lobe lesion that was discovered after he developed worsening headaches and new-onset seizures. The lesion was non-contrast enhancing and T1-hyperintense, which raised suspicion of a LGG; thus follow-up imaging was recommended. Over the next year, the patient was noncompliant with clinic appointments, surveillance brain MRIs, and antiepileptic medications, resulting in eventual admission for generalized tonic-clonic seizures, word-finding difficulties, and right-sided, upper-extremity weakness. MRI at that time demonstrated an enlarged left posterior frontal lobe lesion with mixed solid and cystic components, with heterogeneously enhancing central foci concerning for progression/transformation of the previously noted lesion. Therefore, the patient underwent a left frontal craniotomy with gross total resection. The postoperative course was complicated by an epidural hematoma and wound dehiscence, requiring debridement and intravenous antibiotics.

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Histopathologic evaluation of the resected tumor showed a variably cellular glioma, with focal areas reminiscent of classic PXA transitioning into more cellular and anaplastic foci akin to epithelioid GBM (Figure 3A). Although PXA areas had somewhat fascicular architecture with pleomorphic tumor cells, intermixed eosinophilic granular bodies (Figure 3B, arrow), chronic inflammatory cells (Figure 3B, asterisk), and xanthic cells (Figure 3C), the anaplastic areas had a much more epithelioid phenotype, analogous to an epithelioid variant of GBM with round, discrete cytoplasmic borders (Figure 3D). Notably, the cells in these latter areas did have an intriguing fine microvesicular cytoplasmic quality. Extensive necrosis (including palisading necrosis), marked endothelial hyperplasia, and numerous mitoses were evident. Foci of increased pericellular reticulin deposition were essentially absent and there was a lack of CD34-positive “spider” cells. Immunostaining for mutant *IDH1* R132H was negative. FISH showed polysomy of chromosomes 7 and 10 without *EGFR* amplification or loss of *PTEN* (10q). *MGMT* was unmethylated. *BRAF* V600E was detected through PCR. These collective findings raised differential possibilities of epithelioid GBM arising in a background of anaplastic

PXA versus an overtly anaplastic PXA. We finally top-lined it as a HGG, with a comment discussing the diagnostic conundrum, and favored the former at the time due to its reminiscence to classic PXA in focal areas.

Whether these are 2 distinct entities or a spectrum of the same remains to be seen, although some recent work suggests an overlap based on the genome-wide methylation analysis.¹ Interestingly, considerable methylome heterogeneity was noted despite the unifying feature of common *BRAF* V600E mutations.¹

After a prolonged recovery, standard-of-care concurrent chemoradiation with temozolomide was initiated and completed without incident. Unfortunately, 1 month later, the patient developed purulent drainage from the incision, requiring multiple washouts, then ultimately underwent removal of the bone flap along with a course of intravenous antibiotics. The initial plan was to complete 6 cycles of high-dose adjuvant temozolomide once antibiotics were completed; however, the patient missed clinic appointments over the subsequent 3 months before re-presenting to the hospital with worsening right-sided weakness. Repeat brain MRI revealed new nodular enhancements along the medial aspect of the resection cavity and pachymeningeal nodular enhancement along the inferior left frontal convexity associated with markedly increased FLAIR signal involving the corticospinal tract, consistent with disease progression. The antiangiogenic agent bevacizumab was started in an attempt to reduce the FLAIR signal and preserve motor function.

Over the next 2 months, the patient had multiple admissions for seizures due to medication non-compliance, delaying the initiation of adjuvant temozolomide, although he continued to receive bevacizumab every 2 weeks. The patient did eventually complete 2 cycles of adjuvant temozolomide, although he continued to be noncompliant with antiepileptic drug treatment, resulting in multiple hospitalizations for seizures. Unfortunately, brain MRI after 2 cycles of temozolomide showed progression of the pachymeningeal-based nodular mass along the left frontal convexity (Figure 4A, white arrow). Therefore, dabrafenib (150 mg, twice daily) and trametinib (2 mg, daily) were started while continuing bevacizumab. Remarkably, the patient presented to clinic for follow-up 1 week later and was no longer

Figure 3. Histopathology of the tumor from patient 2, which has areas akin to epithelioid GBM (A, left) and PXA (A, right; HE staining, original magnification x10). Moderately cellular PXA areas are rich in eosinophilic granular bodies (B, arrow) and lymphoplasmacytic cell infiltrate (B, asterisk; HE staining, original magnification x20). Xanthic cells are also focally appreciable (C, arrows; HE staining, original magnification x20). Anaplastic foci with large areas of necrosis and epithelioid cell phenotype of tumor cells in areas similar to epithelioid GBM; interestingly, many of the tumor cells have microvesicular quality (D, arrow; HE staining, original magnification x20). Abbreviations: GBM, glioblastoma; HE, hematoxylin-eosin; PXA, pleomorphic xanthoastrocytoma.

Figure 4. Brain MRI of patient 2 before (A), 4 weeks after (B), and 3 months after (C) treatment with dabrafenib and trametinib. Images are representative axial views from the postcontrast T2-weighted, fluid-attenuated inversion recovery (FLAIR) sequences. The white arrow marks a pachymeningeal-based left frontal lobe lesion. The black arrow indicates area of leptomeningeal gliomatosis, which is resolved on subsequent brain MRI (C).

wheelchair bound, walking independently, with resolving aphasia consistent with a profound clinical response. Consistently, MRI performed 1 month after starting dual-targeted therapy revealed partial regression of the left frontal mass (Figure 4B, white arrow), although increased leptomeningeal enhancement concerning for leptomeningeal gliomatosis was observed (Figure 4B, black arrow), consistent with a mixed response. Regardless, he continued to improve clinically, and follow-up MRI at 3 months demonstrated continued regression of the left frontal mass and improvement in noted leptomeningeal gliomatosis and vasogenic edema (Figure 4C, white arrow). The patient experienced no breakthrough seizures after starting targeted therapy, and thus bevacizumab was discontinued.

Unfortunately, shortly thereafter the patient again became noncompliant with dabrafenib and trametinib, resulting in rapid disease progression and increased vasogenic edema. After a prolonged hospitalization for status epilepticus, the patient declined further treatment and passed away shortly thereafter.

Discussion

Unlike melanoma and thyroid cancer, in which somatic *BRAF* V600E point mutations are present in at least half of cases,²⁻⁴ their reported frequency in adult HGGs (1%–3%)⁵⁻⁸ is comparable to that of other solid tumor types, such as colorectal carcinoma (3%),⁹ NSCLC (3%),¹⁰ ovarian carcinoma (0.5%),¹¹ and squamous cell carcinoma of the head and neck (1.4%–3%).^{12,13} However, it is important to note that *BRAF* mutations are enriched in some

variants of GBM, such as epithelioid GBM, a rare but recently recognized variant of *IDH* wild-type GBMs.¹⁴ Although epithelioid GBMs often lack the common molecular characteristics of adult GBMs, such as *EGFR* amplification or *PTEN* loss, the frequency of *BRAF* V600E mutations in this subgroup is estimated at 50%.^{6,15-18} Likewise, *BRAF* V600E mutations are commonly found in LGGs, such as PXA or ganglioglioma,^{8,19-22} and therefore HGGs arising via malignant transformation from these lesions also possess an increased number of *BRAF* mutations.²³⁻²⁷ Interestingly, in some circumstances, the presence of a *BRAF* mutation may actually drive the transformative process, because *BRAF* V600E mutations appear to be mutually exclusive with *IDH* mutations, suggesting that they may be an alternative oncogenic driver in a subset of *IDH* wild-type LGGs.^{8,20,22,23,25,28-32} However, it is important to note that conclusions from these studies are limited by small sample sizes, although these observations do suggest that patients with GBM, particularly those with GBMs with an epithelioid histology or *IDH* wild-type secondary GBMs, should be routinely screened for the presence of an actionable *BRAF* V600E mutation.

To date, with the exception of one case of pediatric GBM,¹⁶ most case reports describing the successful treatment of *BRAF* V600E–positive gliomas with *BRAF*-targeted therapy involve patients with LGGs.^{16,28,33-42} (Table 1). As such, the role of targeted therapy in adult *BRAF*-mutated HGGs has not been explored. Additionally, all previous reports have been in patients with recurrent or refractory disease following standard radiation and cytotoxic chemotherapy, so the role of targeted therapy in newly diagnosed patients is unclear. As such, this is the first report describing the successful treatment of an adult with a *BRAF* V600E–positive HGG using dual-targeted therapy. Furthermore, we demonstrate for the first time that targeted therapy can safely induce objective and durable clinical responses when used as a first-line agent in patients who are not candidates for aggressive multimodality treatment. Overall, these findings greatly expand on the potential role for these agents in the treatment of *BRAF*-mutated HGGs.

In metastatic melanoma, dual-targeted therapy with combined *BRAF* and MEK inhibition has been shown to reduce the rate of secondary skin cancers

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and the development of resistance.^{43,44} In gliomas, previous studies of targeted therapy have mostly been performed using single-agent BRAF inhibitors (Table 1). Thus, the potential benefit of adding an MEK inhibitor (trametinib or cobimetinib) to targeted therapy had not been evaluated in HGGs. We reasoned that combined dabrafenib and trametinib may be more advantageous given the aggressive nature of the disease. Indeed, both reported patients experienced rapid clinical and radiographic improvement. Although the long-term outcome of dual-targeted therapy could not be evaluated in patient 2 due to treatment noncompliance, patient 1 experienced disease control for approximately 11 months before developing progressive disease, which is consistent with results from phase III studies using these agents in metastatic melanoma.^{43,44} These observations suggest that dual-targeted therapy may be an effective therapeutic option for patients with BRAF-mutated HGGs, including as first-line therapy or if a rapid response is needed. Unfortunately, given the rarity of this patient population, larger clinical trials directly comparing the efficacy of dual-targeted therapy with standard-of-care chemoradiation may not be feasible. Therefore, the decision regarding when to use

targeted therapy will need to continue to be made on a case-by-case basis for the immediate future.

Conclusions

This report describes 2 adult patients with BRAF V600E-positive HGG successfully treated with combined dabrafenib and trametinib therapy. Both patients had significant clinical and radiographic responses, consistent with prior results using single-agent BRAF inhibitors in LGGs. Furthermore, these cases propose several important considerations: (1) routine screening for the presence of BRAF point mutations in adult HGGs should be part of the initial molecular characterization; (2) treatment with targeted therapy in newly diagnosed, BRAF-mutated HGGs is a safe and effective approach, particularly in patients deemed to be poor candidates for aggressive chemoradiation; and (3) combination dabrafenib and trametinib remains safe and efficacious for the treatment of central nervous system disease, even when used with antiangiogenic agents. Although these conclusions need to be validated in larger patient cohorts, the case reports herein provide encouraging proof-of-principle data supporting the pursuit of such studies.

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