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Durable Progression-Free Survival With the Use of BRAF and MEK Inhibitors in Four Cases With *BRAF* V600E-Mutated Gliomas

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Abstract

Introduction: *BRAF* V600 E mutations have been identified in a subset of patients with primary brain tumors. Combination therapy with BRAF and Mitogen-activated protein kinase (MEK) inhibitors (BRAF/MEKi) targeting sequential steps in the MAPK pathway has replaced BRAFi monotherapy as the standard of care in multiple tumors with *BRAF* V600 E mutations, and clinical evidence for this strategy continues to grow in primary brain tumors.
Case series: We describe four patients with *BRAF* V600 E mutated gliomas, including a 21-year-old woman with a ganglioglioma WHO grade I, a 19-year-old man with a pleomorphic xanthoastrocytoma WHO grade III, and 21-year-old and 33-year-old women with epithelioid GBM WHO grade IV, who achieved durable progression-free survival with combination BRAF/MEKi.
Conclusion: Combination of BRAF/MEK inhibition can be a novel, promising approach as targeted therapy in gliomas with *BRAF* V600 E mutations, especially those that are resistant to standard therapy. Our cases, along with other early reports utilizing dabrafenib/trametinib, highlight the importance of somatic next-generation sequencing, particularly in younger patients. Interim results from clinical trials utilizing dabrafenib/trametinib have been promising thus far, and our case series suggests that durable clinical benefit is possible, even in the setting of glioblastoma, WHO grade IV.

Keywords

glioblastoma, BRAF, CNS tumor, brain tumor, cancer, treatment

Introduction

BRAF V600 E mutations have been identified in a subset of patients with primary brain tumors in both pediatric and adult populations, including but not limited to 18% of gangliogliomas (GG), 66% of pleomorphic xanthoastrocytomas (PXA), and 1–2% of glioblastomas (GBM).[1-3] Targeted therapy for *BRAF* V600E-mutated tumors was first attempted with BRAF inhibition (BRAFi) monotherapy in the setting of melanoma in 2010.[4] Over the last decade, combination therapy with BRAF and Mitogen-activated protein kinase (MEK) inhibitors (BRAF/MEKi) targeting sequential steps in the MAPK pathway has replaced BRAFi monotherapy as the standard of care in melanoma following improvements in the 12-month overall survival rate (72% vs 65%) and median progression-free survival (11.4 months vs 7.3 months) with the combination of dabrafenib/trametinib vs vemurafenib monotherapy.[5] In the setting of primary brain tumors,

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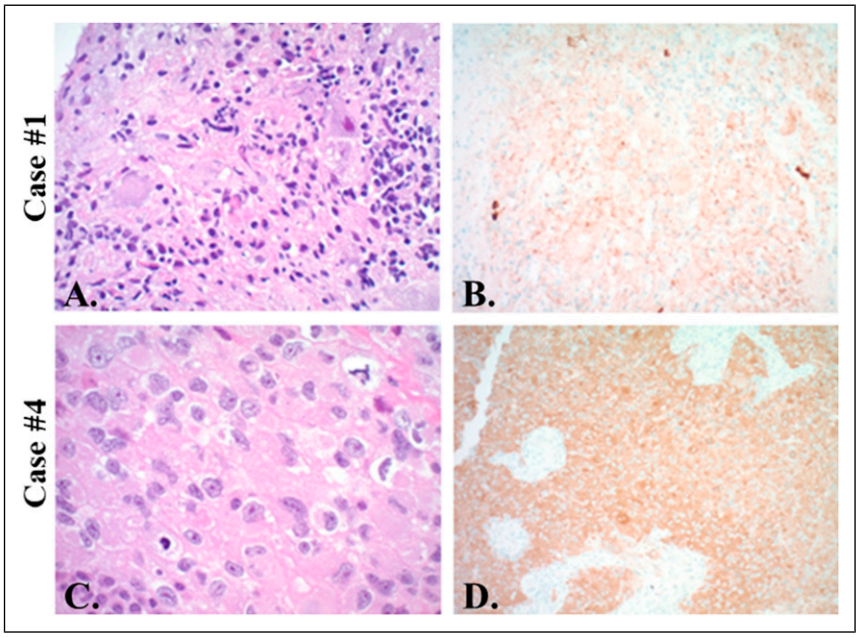

Figure 1. Histopathology. Case 1 shows atypical ganglion cells immersed in disorganized glia (A. H&E, original magnification ×200) with positive immunohistochemistry for mutant BRAF V600 E (B. x200). Case 2 has been published in greater detail previously.[29] Case 4 shows mitotically active atypical epithelioid cells (C. H&E x400) which strongly express mutant BRAF V600 E (D. x200). Case 3 not shown.

vemurafenib monotherapy has been active in low-grade tumors (eg, PXA, WHO grade II), but has been less successful in GBM. Treatment with vemurafenib in the VE-BASKET study resulted in a best response of stable disease in three GBM patients, with two experiencing progression at 3.6 months (censored at the last assessment) and 3.7 months, and one with prolonged stable disease (SD) for 12.9 months.[6] Clinical trials are ongoing to assess the combination BRAF/MEKi for the treatment of low- and high-grade gliomas with encouraging interim data presented at the Society of Neuro-Oncology 2019 Annual Meeting.[7] Among a database of 469 primary brain tumor patients with genomic data entered between April 1, 2013 and November 1, 2018, we identified a cohort of 12 primary glioma patients with *BRAF* V600 E mutations. *BRAF* V600E-positivity was identified by immunohistochemistry (IHC) in 92% (n=11) of patients. All patients had confirmation of *BRAF* V600 E positivity by either next-generation sequencing (n=11) or pyrosequencing (n=1). Among the cohort of 12 *BRAF* V600E-mutated gliomas, we identified four patients treated with dabrafenib/trametinib. Herein, we describe those four patients with *BRAF* V600 E mutated gliomas who achieved durable progression-free survival (PFS) utilizing targeting therapy with combination BRAF/MEKi.

Case #1

A 21-year-old woman was found to have an enhancing mass with a cystic component in the upper cervical cord involving the medulla oblongata on Magnetic Resonance Imaging (MRI) after presenting with a syncopal episode. She underwent biopsy of the lesion at an outside hospital. Pathology showed mild chronic inflammatory disease; however, upon review at Moffitt Cancer Center (MCC), pathology revealed ganglioglioma, World Health Organization (WHO) grade I (Figure 1), *IDH1* wild type by IHC, ATRX-retained, and positive for *BRAF* V600 E mutation by IHC. She remained stable radiographically on surveillance scans. However, 12 months after initial diagnosis, a repeat MRI scan showed increase in tumor growth both in the enhancing and the non-enhancing regions involving both the brainstem and the upper cervical cord (Figure 2). The enhancing part of the upper largest diameter of the brainstem lesion increased to 1.48 cm (compared to prior measuring 1.17 cm) on axial view (Figures 2A and 2B) and to 1.42 42 x 1.43 cm (compared to prior measuring 1.06 ×06 x .83 cm) on sagittal view (Figures 2G and 2H).

Given the superior efficacy of concurrent BRAF/MEKi therapy in other cancer types and gliomas with *BRAF* V600 E mutation,[8–26] she was immediately started on dabrafenib 150 mg per oral (**PO**) twice a day (**BID**) with trametinib 2 mg PO daily added one month later due to insurance issues. MRI performed 3 months later showed a decrease in the size of the enhancing tumor involving the right brainstem, right cervical medullary junction, and dorsal aspect of the cervical cord at the level of C2. Serial imaging showed SD was maintained for 9 months after the initiation of BRAF/MEKi targeted therapy.

Unfortunately, soon after there was radiographic evidence of disease progression and therapy was changed to

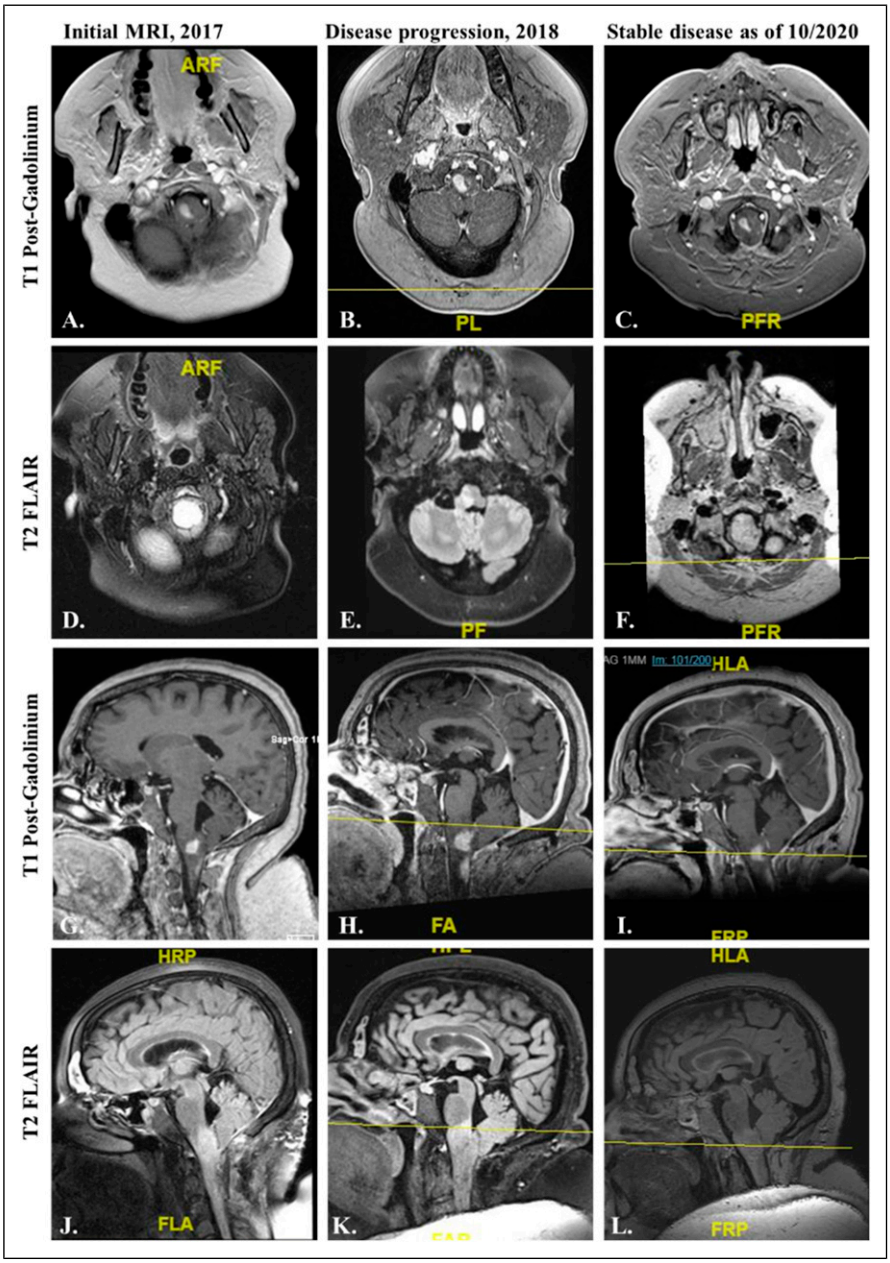

Figure 2. Magnetic Resonance Imaging of the brain of case #1 at initial diagnosis and before and after treatment with BRAF/MEK inhibitors. On 05/2017, initial MRI brain showed interval tumor growth of the ganglioglioma involving brainstem and upper cervical spinal cord as seen with increased enhancing tumor and T2 signal (A, D, G, J.). The enhancing part of the upper largest brainstem lesions measures 1.17 cm on axial view (A.) and 1.06 x 0.83 cm on sagittal view (G.). On 05/2018, MRIs showed disease progression with increase in the size of the lesions, with the enhancing part of the upper brainstem lesion now measuring 1.48 cm in axial view (B.) and 1.42 x 1.43 cm in sagittal view (H.) (B, E, H, K.). BRAF/MEK inhibitors were added. Most current MRIs as of 10/2020 show overall smaller in the size of the lesions, with the enhancing part of the upper brainstem lesion now measuring 1.32 cm in axial view (C.) and 1.10 x 0.80 cm in sagittal view (L.) (C, E, I, L.). A–C and G–L = T1 Post-Gadolinium. D–F and J–L = T2 FLAIR sequences.

encorafenib 450 mg PO daily and binimetinib 45 mg PO BID, based upon higher dosing and potentially greater CNS penetrance, while minimizing toxicity. Chloroquine 500 mg PO daily was also added based on early evidence supporting inhibition of autophagy as a potential strategy for overcoming MAPK-pathway resistance.[27,28] She had a good response to treatment. After 5 months, the treatment was held due to hyperglycemia. She remained on surveillance with serial scans. Since the treatment was held, she has remained with clinical and radiographic SD ongoing at 29 months after initial start of BRAF/MEKi and 18 months after addition of chloroquine to BRAF/MEKi therapy (Figure 2).

Case #2

A 19-year-old, previously healthy man was found on MRI of the brain to have a large right-sided lesion in the parieto-temporal lobes, with surrounding vasogenic edema and a right-to-left midline shift. He underwent a subtotal surgical resection and was diagnosed with GBM at an outside hospital. He was started on standard treatment with radiation therapy (RT) and concomitant temozolomide (TMZ); however, given tumor recurrence 4 months later, he underwent a second maximal safe gross total resection. Pathology was consistent with a glioma resembling an anaplastic PXA, WHO grade III–IV, non-infiltrating, with a high mitotic index, IDH1 R132H-negative by IHC, negative for EGFRviii and 1p/19q co-deletion, and positive for *BRAF* V600 E mutation by IHC. He was monitored with serial MRI scans and had SD on radiographic surveillance.

Seventeen months following his second resection, an MRI of the brain identified a small increase in the size of his tumor. MRI perfusion scan showed hyperperfusion supporting the diagnosis of recurrent tumor. Based on this, combination therapy with dabrafenib 150 mg PO BID and trametinib 2 mg PO daily was initiated. Imaging remained stable on serial MRIs for 14 months, at which point slight progression was noted on MRI and chloroquine 500 mg PO daily was added to his therapy regimen.[29] The patient remained stable for an additional 21 months with the addition of chloroquine to his BRAF/MEKi regimen. Recently, the patient began to progress (as confirmed on MRI brain with MRI perfusion scans) and underwent resection of his anaplastic PXA, WHO grade III-IV, after approximately 35 months on targeted therapy. This is an update to a case that has been published in greater detail previously.[29]

Case #3

A 21-year-old woman presented with complaints of dizziness and severe headaches. Her primary care physician ordered an MRI brain, which showed a left frontal 1.2 cm size lesion. Due to these findings, she was advised to go the emergency department. She was admitted at an outside hospital, where an MRI brain/spectroscopy was performed, confirming the 1.2 cm left frontal rim enhancing cystic lesion with restricted diffusion, abutting the superior margin of the insula. She was evaluated by a neurosurgeon who recommended repeat MRI brain in 1 month. The repeat scans showed an increase in the size of the lesion. A left frontal craniotomy with gross total tumor resection was performed at MCC. Pathology showed an epithelioid GBM, WHO grade IV, negative for *IDH1* R132H by IHC, ATRX-retained, negative for MGMT promoter methylation, and positive for *BRAF* V600 E confirmed by FoundationOne® assay.

She completed treatment with RT and TMZ followed by maintenance TMZ. After 4 cycles of maintenance TMZ, MRI brain showed two new subcentimeter enhancing nodules around the resection cavity with a mild to moderate increased in vasogenic edema on T2 FLAIR sequence, and no mass effect. These findings were concerning for tumor recurrence. TMZ was switched to BRAF/MEKi with dabrafenib 150 mg PO BID and trametinib 2 mg PO daily. She was not on steroids and given no mass effect or concern for treatment-related changes was not started on steroids or any other treatment for radiation necrosis. Subsequent MRI brain 2 months later showed a reduction in the size of the tumor. She has remained clinically and radiographically stable on this treatment at 16 months after initiation of targeted therapy.

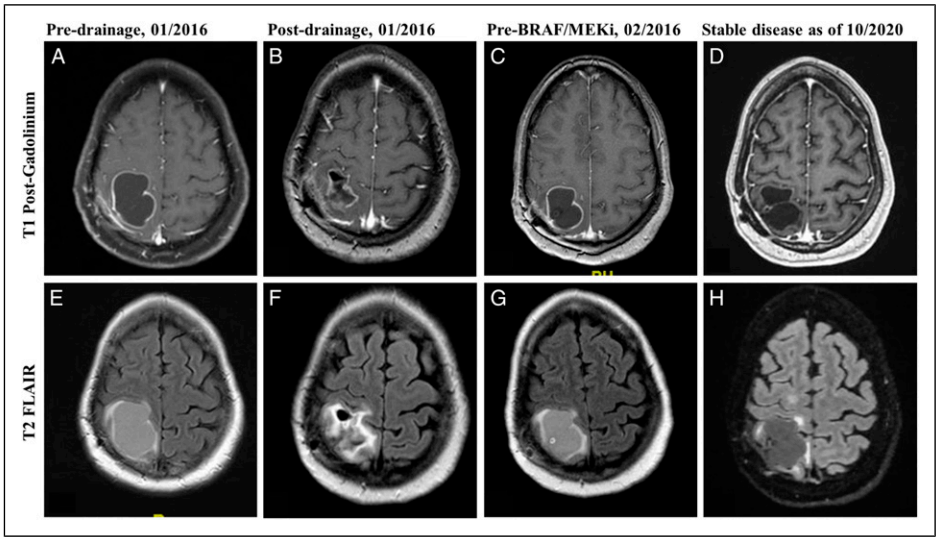

Figure 3. Magnetic Resonance Imaging of the brain of case #4 pre- and post-cystic drainage, and before and after treatment with BRAF/MEK inhibitors. On 01/2016, MRI brain performed pre- (A. and E.) and post-surgical drainage of the cystic component of the lesion and before starting treatment with maintenance temozolomide (B. and F.). On 02/2016, MRI with rapid refilling of the cystic component of the lesion and before starting treatment with BRAF/MEK inhibitors (C. and G.). Most current MRIs as of 10/2020 show stable disease since started on BRAF/MEK inhibitors, without requiring further surgical drainage (D. and H.). A–D = T1 Post-Gadolinium. E–H = T2 FLAIR sequences.

Table 1. Literature review of low-grade and high-grade gliomas treated with combination therapy with BRAF/MEKi or monotherapy with BRAFi.

Citation	Age (years)	Sex	Diagnosis	WHO grade	Line of therapy	Treatment	Best response	Rx duration (months)
Patient case #1	21	F	Ganglioglioma	I	2nd	Dabraf+tramet	SD	14[a]
Del Bufalo et al[20]	2.5	M	Ganglioglioma	I	2nd	Vemuraf	PR	54
Del Bufalo et al[20]	4.5	NR	Ganglioglioma	I	1st	Vemuraf	CR	40
Aguilera et al[22]	8	M	Ganglioglioma	I	1st	Vemuraf	PR	14 [a]
Del Bufalo et al[20]	7.4	NR	Ganglioglioma	I	1st	Vemuraf	SD	13
Chamberlain et al[23]	45	M	Ganglioglioma	I	2nd	Dabraf	PR	10
Lassaletta et al[24]	2 mo	F	Hypothalamic chiasmatic glioma	I	2nd	Dabraf	PR	10
Chamberlain et al[23]	34	M	Ganglioglioma	I	2nd	Dabraf	SD	7
Chamberlain et al[19]	26	F	Ganglioglioma	I	2nd	Dabraf	SD	4
Del Bufalo et al[20]	1 mo	NR	Ganglioneurocytoma	I	1st	Vemuraf	PD	3
Del Bufalo et al[20]	10	NR	Ganglioglioma	I	1st	Vemuraf	Insuf. F/up	2
Del Bufalo et al[20]	9	NR	PXA	II	1st	Vemuraf	PR	30
Chamberlain et al[19]	53	M	PXA	II	3rd	Vemuraf	PR	10
Chamberlain et al[19]	47	F	PXA	II	3rd	Vemuraf	SD	6
Chamberlain et al[19]	34	F	PXA	II	3rd	Vemuraf	SD	4
Usubalieva et al[21]	35	F	PXA	II	1st	Dabraf	PR	3
Patient case #2	19	M	Anaplastic PXA	III	2nd	Dabraf+tramet	SD	35[a]
Toll et al[8]	4	F	Anaplastic ganglioma	III	1st	Dabraf+tramet	PR	23[a]
Brown et al[11]	21	F	Anaplastic PXA	III	1st	Dabraf+tramet	PR	22[a]
Toll et al[11]	13	M	Anaplastic astroblastoma	III	2nd	Dabraf+tramet	CR	20
Brown et al[11]	48	F	Anaplastic PXA	III	4th	Dabraf+tramet	PR	8[a]
Smith-Cohn et al[26]	23	F	Anaplastic PXA	III	2nd	Dabraf+tramet	PR	3
Burger et al[15]	24	M	Anaplastic PXA	III	2nd	Dabraf	CR	27[a]
Bautista et al[17]	1.5	F	Anaplastic ganglioma	III	5th	Vemuraf	PR	20[a]
Burger et al[15]	50	M	Anaplastic PXA	III	3rd	Dabraf	PR	8[a]
Bautista et al[17]	6	M	Anaplastic ganglioma	III	2nd	Vemuraf	PR	3
Lee et al[18]	41	M	Anaplastic PXA	III	2nd	Vemuraf	PR	3[a]
Leaver et al[16]	39	M	Anaplastic PXA	III	1st	Vemuraf	PR	2
Chamberlain et al[19]	43	M	Anaplastic PXA	III	3rd	Vemuraf	PD	2
Bautista et al[17]	9	F	Anaplastic astrocytoma	III	4th	Vemuraf	PD	0.5
Patient case #4	33	F	Epithelioid GBM	IV	2nd	Dabraf+tramet	SD	53[a]
Toll et al[8]	12	F	HGG with epithelioid morphology	IV	2nd	Dabraf+tramet	PR	32[a]
Johanns et al[9]	28	F	Epithelioid GBM	IV	1st	Dabraf+tramet	PR	11
Patient case #3	21	F	Epithelioid GBM	IV	2nd	Dabraf+tramet	SD	16[a]
Woo et al[10]	22	F	Epithelioid GBM	IV	1st	Dabraf+tramet	PR	7
Woo et al[10]	22	F	Epithelioid GBM	IV	1st	Vemuraf+cobimet	SD	5.5
Johanns et al[9]	24	M	Epithelioid GBM	IV	2nd	Dabraf+tramet	PR	3[b]
Smith-Cohn et al[26]	47	M	Epithelioid GBM	IV	3rd	Dabraf+tramet	PD	1
Beba Abadal et al[12]	34	F	GBM	IV	3rd	Vemuraf	SD	11
Ceccon et al[13]	27	M	Epithelioid GBM	IV	4th	Dabraf	SD	10
Robinson et al[14]	9	M	Epithelioid GBM	IV	3rd	Vemuraf	PR	6[a]
Burger et al[15]	25	M	Glioblastoma, IDH-wt	IV	3rd	Dabraf	PR	3[a]
Leaver et al[16]	26	M	Epithelioid GBM	IV	1st	Vemuraf	PD	0.5

[a]Treatment ongoing
[b]Non-adherent to treatment.
Abbreviations: F = female, M = male, GBM = glioblastoma, PXA = pleomorphic xanthoastrocytoma, Dabraf = dabrafenib, dabraf+tramet = dabrafenib/trametinib, vemuraf = vemurafenib, vemuraf+vobemet = vemurafenib/vobimetinib, CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, NR = not reported, insuf. f/up = insufficient follow-up.
Keywords searched: glioma, primary brain tumor, BRAF, MEK, targeted, vemurafenib, dabrafenib, encorafenib, cobimetinib, trametinib, and binimetinib (Date range: January 2000 to December 2019).

Case #4

A 33-year-old woman with a past medical history of Graves' disease, presented with a 3-year history of worsening episodes of left eye vision loss. An MRI of the brain showed a cystic right parietal mass with peripheral enhancement measuring 5.5 x 4.4 x 5.5 cm and a nodular enhancing region. She underwent a right parietal craniotomy and pathology confirmed an epithelioid GBM, WHO grade IV (Figure 1), negative for *IDH1* R132H by IHC and confirmed *IDH1/2* wild-type by NGS, ATRX-retained, MGMT promoter-methylated, negative for 1p/19q co-deletion, and positive for *BRAF* V600 E mutation by FoundationOne® assay (see supplementary Table 1 for complete NGS results from FoundationOne®). She was started on standard therapy with RT and TMZ for six weeks. Shortly thereafter, she developed a symptomatic increase in the size of the cystic region of the lesion and was taken back to the operating room for drainage, with quick refilling requiring a second drainage in the operating room a month later (Figure 3). She had been on dexamethasone 4 mg total a day during this time to help control her symptoms.

She subsequently progressed after 2 cycles of maintenance TMZ, with MRI brain showing interval increase size of bilobed or 2 adjacent areas of ring enhancement in the right parietal lobe deep to the craniotomy site measuring now 5.0 x 3.3 cm compared to previous MRI measuring 4.2 x 2.7 cm, with persistent surrounding increased T2 FLAIR signal consistent with vasogenic edema, which was consistent with recurrent GBM. TMZ was discontinued and she was started on dabrafenib 150 mg PO BID and trametinib 2 mg PO daily. Dexamethasone was tapered off. She had a subsequent immediate response to therapy with interval decrease in the size of the right frontoparietal epithelioid GBM compared to prior MRI brain a month earlier, consistent with interval response to therapy. The patient remains clinically and radiographically stable at this time, 53 months after initiating treatment with BRAF/MEKi.

Discussion

Primary brain tumors are a heterogeneous group of neoplasms that range from relatively slow-growing (ie, pilocytic astrocytoma) to aggressive and invasive tumors (ie, GBM WHO grade IV) with an overall poor prognosis.[30] The standard of care for GBMs remains limited, which includes maximal safe surgical resection with subsequent RT and concomitant TMZ, followed by 6 cycles of adjuvant TMZ.[31,32] Second-line therapy with bevacizumab was shown to improve PFS, but no improvement in overall survival was achieved.[33] Other therapies following the standard first-line of TMZ have provided only modest benefit with much need remaining for improved therapy options.[34]

BRAF V600 E mutations have been identified in a subset of patients with melanoma (35 to 50% of cases),[35] non-small cell lung cancer (**NSCLC**, 1% to 2%),[36] colorectal cancer (8% to 15%),[37] and anaplastic thyroid cancer (20% to 50%).[38] This mutation has also been found in primary brain tumors among distinct histological subtypes including 9% of pilocytic astrocytomas, 18% of gangliogliomas, 66% of PXA, 90% of papillary craniopharyngiomas, and 1% to 2% of GBM IDH wild type.[1-3] Notably, there is an enrichment for *BRAF* V600 E alterations in approximately 50% of the GBM epithelioid subtype,[39] which typically carry a poorer prognosis with a median survival of 6.3 months.[40] The potential predictive value of BRAF alterations in this GBM subtype underscores the importance of genomic testing and the critical need to find more effective therapeutic options.

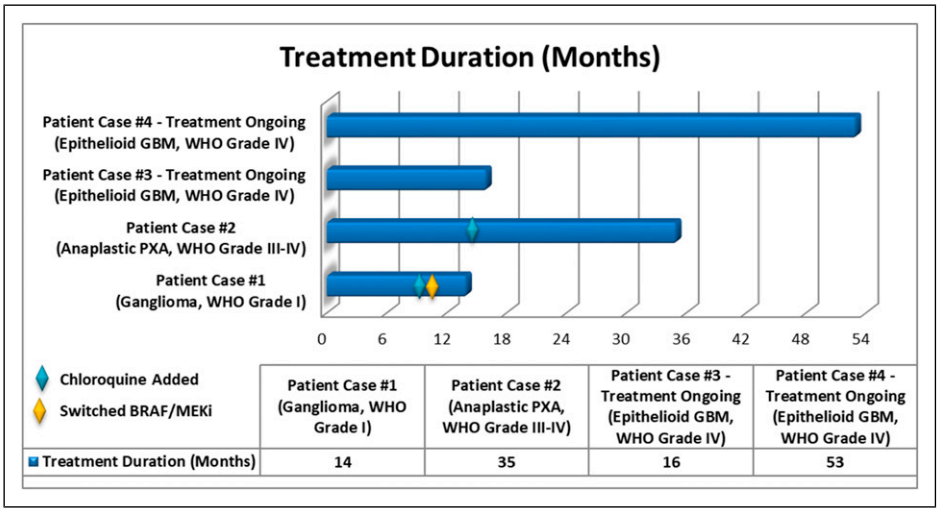

Figure 4. Treatment duration for BRAF V600E-mutant gliomas treated with targeted therapy. Patients were treated with dabrafenib plus trametinib. Patient cases #1 and #2 had chloroquine added to their regimen at approximately 9 months and 14 months, respectively. Patient cases #3 and #4 are ongoing with treatment at 16 months and 53 months, respectively.

Table 2. Molecular profile of BRAF V600E-mutant GBM cases treated with BRAF/MEKi. Highlighted are the mutations present in the two patients with epithelioid GBM WHO grade IV.

Patient case #3—ongoing with treatment at 16 months				Patient case #4—Ongoing with treatment at 53 months			
Gene	Alteration	MAF/Copy number	Location	Gene	Alteration	MAF/Copy number	Location
BRAF	V600 E	38.3%	7q34	BRAF	V600 E	32.0%	7q34
CDKN2A	Loss	0	9p21	CDKN2A	Loss	0	9p21
CDKN2B	Loss	0	9p21	CDKN2B	Loss	0	9p21
PIK3CG	R49S	40.6%	7q22.3	PIK3CG	Amplification	7	7q22.3
BRD4	P482 L	61.3%	19p13.1	CDK6	Amplification	8	7q21-q22
ZNF703	A401_H402ins PTHLGGSSCSTCSA	34.9%	8p11.23	PIK3R1	T576_L581del	28.0%	5q13.1
CREBBP	A1907 T	48.1%	16p13.3	HGF	Amplification	8	7q21.1
CREBBP	Q771 R	49.0%	16p13.3	U2AF1	Amplification	8	21q22.3
FANCA	V121 L	51.1%	16q24.3	SNCAIP	Amplification	8	5q23.2
PREX2	G382S	44.2%	8q13.2	SMO	Amplification	7	7q32.3
PRKDC	Q947 L	45.1%	8q11	RUNX1	Amplification	8	21q22.3
				RICTOR	Amplification	8	5p13.1
				RAC1	Amplification	7	7p22
				PIK3R1	Amplification	8	5q13.1
				PIK3CG	Q134 L	7	7q22.3
				MSH6	K1358fs*2	29.0%	2p16
				MLL3	P3468 L	58.0%	7q36.1
				MET	Amplification	7	7q31
				MAP3K1	Amplification	8	5q11.2
				MAGI2	Amplification	8	7q21
				MLL3	Amplification	7	7q36.1
				KEL	Amplification	7	7q33
				INHBA	Amplification	7	7p15-p13
				IL7R	Amplification	8	5p13
				IKZF1	Amplification	7	7p12.2
				GRM3	Amplification	8	7q21.1-q21.2
				GABRA6	Amplification	8	5q34
				FGFR1	S134D	49.0%	8p11.23-p11.22
				FGF10	Amplification	8	5p13-p12
				EZH2	Amplification	7	7q35-q36
				ERG	Amplification	8	21q22.3
				EPHA3	E265 G	48.0%	3p11.2
				EGFR	Amplification	7	7p12
				BRCA2	R118 C	58%	13q12.3
				BRAF	Amplification	7	7q34
				APC	Amplification	7	5q21-q22

In the setting of primary brain tumors, the VE-basket trial recently demonstrated the feasibility of targeting *BRAF* V600E-mutated gliomas with vemurafenib monotherapy.[6] The objective response rate (**ORR**) for the PXA patients treated with vemurafenib monotherapy was 42.9%. In contrast, the ORR for the malignant glioma subgroups (ie, anaplastic astrocytoma and GBM) was only 9.1%. The authors concluded that responses to vemurafenib monotherapy were observed across all glioma subsets, with the strongest signal observed in patients with lower-grade gliomas, particularly the PXA subgroup.[6]

Other reports have also suggested that high grade gliomas may not achieve the same level of disease control from BRAFi monotherapy that has been seen in low-grade gliomas.[8–26] In contrast, there are multiple documented cases with *BRAF* V600 E mutant low-grade gliomas and high-grade gliomas resistant to RT and TMZ with durable responses to concurrent BRAF/MEKi therapy (see Table 1). The superiority of combination BRAF/MEKi treatment has been clearly demonstrated in other cancer types and our cases, along with other small case series reported (Table 1), suggest that combination BRAF/MEKi may provide the additional MAPK pathway

inhibition needed to see durable responses in patients with grade III and Grade IV gliomas (Figure 4).

The potential for publication-bias remains with described clinical case series of benefit with targeted treatment, but in the setting of rare molecular subsets of cancer they offer important early evidence of clinical activity in rare molecular subsets of cancer. Clinical trials assessing combination dabrafenib/trametinib for both low- and high-grade gliomas are ongoing (NCT02034110) and interim reports have been promising, with an ORR of 62% and 29% in low- and high-grade gliomas, respectively. Durable clinical benefit was also seen in subset of patients with a median treatment duration of 19.5 months (range, 1 to 55 months) and 10.6 months (range, 1 to 43 months) in patients with low- and high-grade gliomas, respectively.[7]

Patients with epithelioid GBM have historically had a poor prognosis; however, subsets of epithelioid GBM may have a more favorable prognosis than others.[41] Additional work is needed to characterize the response to combination BRAF/MEKi in each of these subsets. The patients with epithelioid GBM in our small series, treated with BRAF/MEKi, have both demonstrated stable clinical and radiographic disease, with a duration of response of 16 months and 53 months, respectively, both ongoing at the time of publication.[8-24] To the best of our knowledge, case 4 in this small series represents the longest duration of clinical benefit from BRAF/MEKi that has been reported to date. Although of unclear significance, the two patients with epithelioid GBM share genetic alterations that may be relevant in the context of a favorable response to treatment with combination BRAF/MEKi and should be explored in future studies (Table 2). Our cases, along with other early reports utilizing dabrafenib/tramentinib, provide evidence of sustained clinical benefit from combined BRAF/MEKi therapy even in the setting of high-grade gliomas.

All patients who underwent RT, except case 4, had MRI perfusion performed in addition to the MRI brain to differentiate tumor progression vs treatment-related changes. Case 4 was deemed to have tumor progression based on radiographic appearance, which was further supported by her immediate response clinically and radiographically following treatment with BRAF/MEKi, without the need for dose appropriate glucocorticoids or other therapy for radiation necrosis (ie, bevacizumab). MRI changes observed prior to starting BRAF/MEKi being due to treatment-related changes remain a possibility. Nevertheless, the fact that a patient with epithelioid GBM has remained stable for up to 53 months after starting BRAF/MEKi is noteworthy.

It is worth noting that the ganglioglioma and anaplastic PXA patients had chloroquine added to their regimen of BRAF/MEKi at early signs of progression. Chloroquine was added based upon what was perceived as a relatively low risk of adverse events and promising early clinical data suggesting that autophagy inhibition may help to overcome resistance to targeted treatment with BRAFi.[29,42-44]

This small case report series has several limitations. These include being unable to generalize to a larger cohort of patients with similar diseases. In addition, it is difficult to determine a cause and effect relationship in these independent, single cases with different histopathological features and WHO grades. Prospective clinical trials are needed to better evaluate the effectiveness of BRAF/MEKi in patients with gliomas. Nevertheless, the positive responses to treatment with BRAF/MEKi seen in these patients can lead to the generation of new hypotheses regarding the pathophysiology of these diseases, and allow the expansion of successful new therapies, when prospective studies are not feasible.

Conclusion

The combination of BRAF/MEK inhibition has the potential to offer clinical benefit in both low-grade and high-grade gliomas that historically have not responded as well to BRAFi monotherapy. Our cases, along with other early reports utilizing dabrafenib/trametinib, highlight the importance of somatic next-generation sequencing, particularly in younger patients. Interim results from clinical trials of dabrafenib/trametinib have been promising thus far, and our case series suggests that durable clinical benefit is possible, even in the setting of glioblastoma, WHO grade IV.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Ethical Approval

Our study was approved by the Advarra Ethics Committee (no. Pro00031026, IRB protocol MCC 19859). A waiver of consent was granted for retrospective chart review in accordance with the Declaration of Helsinki and the 21st Century Cures Act.

Informed Consent

All of the patients provided a written informed consent for their information to be published in the current study, except for case #3 who moved out of state and was lost to follow-up. MRI brain and pathology imaging from case #3 were excluded from this study given inability to obtain written informed consent.

Data Availability

All data analyzed during this study are included in this article.

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