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Rapid response to BRAF/MEK inhibitor therapy within 2 weeks for high-grade glioma with leptomeningeal metastasis: illustrative case

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BACKGROUND High-grade gliomas, particularly isocitrate dehydrogenase–wildtype glioblastomas (GBMs), are highly aggressive brain tumors with limited treatment options and poor outcomes. A subset of these tumors, including epithelioid GBM, can harbor the BRAF V600E mutation, which drives tumor growth via persistent activation of the RAS/MAPK signaling pathway. Recently, the combination of dabrafenib (BRAF inhibitor) and trametinib (MEK inhibitor) has been approved for treating inoperable solid tumors with this mutation.

OBSERVATIONS The authors present the case of a 51-year-old man with epithelioid GBM harboring the BRAF V600E mutation who developed early leptomeningeal metastasis (LMM) following standard therapy with surgery, temozolomide, and radiotherapy. Owing to disease progression, he was treated with dabrafenib and trametinib. Remarkably, the patient showed rapid clinical and radiographic improvement within 2 weeks of treatment initiation. MR images demonstrated significant reduction in tumor-associated edema and contrast enhancement. At the 28-week follow-up, the patient achieved near-complete radiographic remission without notable adverse effects.

LESSONS This case highlights the potential of BRAF/MEK inhibitor therapy to significantly improve outcomes in patients with aggressive gliomas and LMM, conditions typically associated with extremely poor prognosis. Further studies are needed to validate the long-term efficacy and safety of this targeted therapeutic approach in similar cases.

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KEYWORDS BRAF V600E; dabrafenib; glioblastoma; leptomeningeal metastasis; trametinib

High-grade gliomas, particularly those with wildtype isocitrate dehydrogenase (IDH) variation, rank among the tumor types with the poorest prognoses.[1] These malignancies generally have significantly worse patient outcomes than their mutant counterparts.[2] Glioblastomas (GBMs), a challenging subset of these tumors, are notorious for their recurrent and progressive nature that also generally results in poor prognoses.[1] The median overall survival (OS) of patients with recurrent GBMs is < 1 year, and no standard of care has been established for this clinical scenario.[3,4] *BRAF* gene mutations can promote the proliferation of tumor cells by continuously activating the RAS/MAPK signaling pathway.[5] In particular, the BRAF V600E mutation is occasionally detected in various CNS tumors, including epithelioid GBM, pleomorphic xanthoastrocytoma (PXA), anaplastic PXA, and ganglioglioma.[6] Notably, the combination therapy of trametinib and dabrafenib was approved by the US Food and Drug Administration in 2022 for use in inoperable solid tumors with BRAF V600E mutations, and a similar approval was granted in Japan in 2023. This marks a significant advancement in the field and suggests a potential paradigm shift in the treatment strategies for brain tumors harboring BRAF mutations. The incidence of leptomeningeal metastasis (LMM) in gliomas is estimated to be 4%.[7] Patients with GBMs who develop LMM have a median OS of 3.8–4.7 months,[7] underscoring the extremely poor prognosis of this condition. Owing to the scarcity of effective treatments, LMM has predominantly been managed through the intrathecal administration of cytotoxic agents, such as methotrexate, or spinal irradiation.[7] Herein, we report the case of a patient with BRAF V600E–mutant epithelioid GBM who developed LMM early in the initial treatment phase following surgery, temozolomide (TMZ), and radiotherapy. He then received combination therapy with dabrafenib and trametinib, which demonstrated early symptomatic and radiographic improvements. Our

ABBREVIATIONS FLAIR = fluid-attenuated inversion recovery; GBM = glioblastoma; IDH = isocitrate dehydrogenase; LMM = leptomeningeal metastasis; OS = overall survival; POD = postoperative day; PXA = pleomorphic xanthoastrocytoma; SOL = space-occupying lesion; TCGA = The Cancer Genome Atlas; TMZ = temozolomide.

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findings suggest that this combination therapy has the potential to be an effective treatment option for refractory high-grade gliomas with LMM, highlighting the need for further clinical evaluations of its long-term efficacy and broader applicability.

Illustrative Case

Preoperative Course

A 51-year-old man who was previously in good health and had no significant family medical history was evaluated in our facility for a minor head trauma. During the assessment, a space-occupying lesion (SOL) was incidentally discovered in the left lateral ventricular trigone. The patient exhibited mild aphasia but had no other neurological symptoms and showed no signs of altered consciousness or headache. Diagnostic imaging revealed a lesion centered on the left ventricular trigone, extending along the ventricular walls. CT imaging showed a calcified mass, and gadolinium-enhanced MRI characterized the SOL as having uneven enhancement and irregular edges (Fig. 1A–F). The lesion obstructed the lateral ventricle, leading to dilation of the temporal horn. The results of advanced imaging techniques, such as MR spectroscopy and amide proton transfer imaging, strongly suggested that the lesion was malignant. Two weeks after the patient's admission to the hospital, follow-up MRI indicated that the lesion had increased in size, suggesting a high degree of malignancy. This finding triggered the planning of a craniotomy for tumor resection.

Surgery

The surgery was performed using a neuronavigation system (Brainlab). The patient was positioned supine with their head rotated 60° to allow for adequate exposure of the left frontotemporal region. A left frontotemporal craniotomy was performed using a middle temporal approach to access the lesion in the left temporal lobe. The lesion was pinkish-gray and highly vascular (Fig. 2A). Fluorescent visualization with 5-aminolevulinic acid showed strong positivity, indicating active tumor metabolism (Fig. 2B). The lesion was infiltrative with indistinct borders, making it difficult to differentiate it from the surrounding normal brain tissue. Rapid intraoperative pathology confirmed the diagnosis of high-grade glioma. Although postoperative MRI revealed a slight residual enhancing lesion within the ventricular walls, near-total resection was achieved (Fig. 2C). A new upper-right quadrant anopia was noted postoperatively; however, no other new complications were noted.

Postoperative Course and Subsequent Management

On pathological examination, the tumor was diagnosed as a high-grade glioma, specifically identified as an epithelioid GBM (Fig. 2D). Immunohistochemical staining confirmed the tumor was partially positive for glial fibrillary acidic protein, diffusely positive for Olig2, and IDH R132H negative, BRAF V600E positive (Fig. 2E), with a Ki-67 labeling index of 20%. Radiotherapy, in conjunction with TMZ at a dosage of 75 mg/m^2, was initiated on postoperative day (POD) 24, with a total radiation dose of 60 Gy delivered in 30 fractions. On POD 56, follow-up MRI revealed multiple small tumor masses with extensive dural enhancement and edema in the left frontal and temporal lobes, as well as enhanced contrast visibility within the resection cavity of the left temporal horn, all of which were considered indicative of LMM (Fig. 3A–D). Despite the administration of combined radiological and chemotherapeutic regimens, the tumor rapidly progressed to progressive disease. Other remote progression was ruled

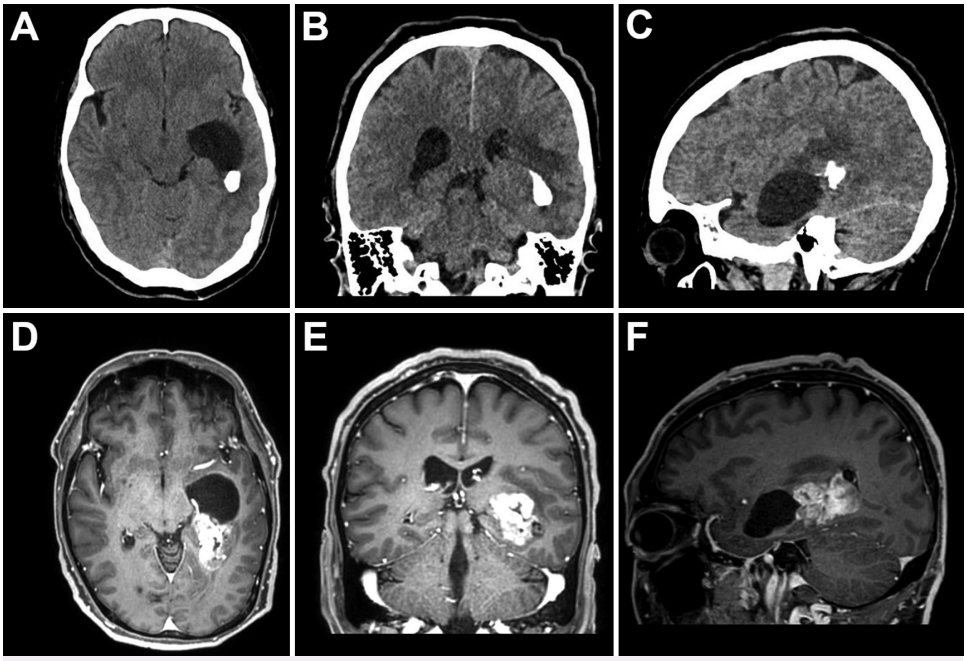

FIG. 1. Preoperative image findings. Preoperative axial (**A**), coronal (**B**), and sagittal (**C**) CT scans showing a calcified mass in the left temporal triangular region, leading to localized dilation of the inferior horn of the left lateral ventricle. Preoperative axial (**D**), coronal (**E**), and sagittal (**F**) MR images showing a heterogeneously enhancing lesion with irregular margins and indistinct boundaries, indicative of an infiltrative process.

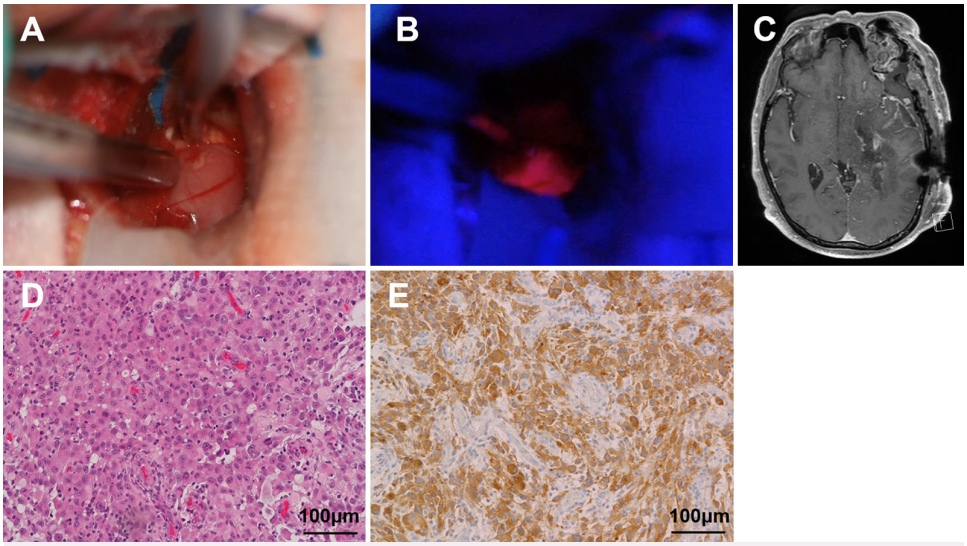

FIG. 2. Intraoperative findings, postoperative imaging, and histopathological findings of the resected tumor. **A:** Intraoperative photograph showing a pinkish-gray, highly vascularized lesion with indistinct margins relative to the surrounding tissue, indicating an infiltrative nature. **B:** The lesion exhibited strong fluorescence under 5-aminolevulinic acid guidance, indicating a high degree of tumor infiltration. **C:** Postoperative axial MR image showing near-total resection of the contrast-enhancing lesion with no significant residual tumor. **D:** H&E staining (magnification ×200). The lesion consists of epithelioid cells with eccentric nuclei, prominent nucleoli, and a round eosinophilic cytoplasm. Cytoplasmic inclusions were sporadically observed. **E:** Epithelioid cells were immunohistochemically positive for BRAF V600E (magnification ×200).

out based on CSF analysis, spinal MRI, and whole-body CT findings. Given the presence of the BRAF V600E mutation, a treatment plan including dabrafenib and trametinib was initiated following the discontinuation of TMZ on POD 57. Radiotherapy was administered as scheduled.

Administration of Dabrafenib and Trametinib

Following a diagnosis confirmed by targeted DNA examination via polymerase chain reaction, which revealed the presence of the *BRAF* V600E mutation in the tumor (as immunohistochemical staining alone does not meet the criteria for confirming this mutation in Japan), treatment with dabrafenib and trametinib was initiated on POD 74. By POD 81, 8 days after the patient was started on these oral medications, MRI showed no change in the enhancing lesion but a significant reduction in the fluid-attenuated inversion recovery (FLAIR) hyperintensity regions in the left frontal and temporal lobes. Further MRI performed on POD 88, 15 days after the initiation of combination therapy, demonstrated a reduction in the dural enhancement within the left frontal lobe, with further reductions in the FLAIR hyperintensity regions of the left frontal and temporal lobes (Fig. 3E–H). No significant adverse effects, such as fever, gastrointestinal distress, or dermatological symptoms, were observed following the initiation of dabrafenib and trametinib. Blood tests revealed no apparent adverse events. The patient was discharged on POD 89 to continue medication on an outpatient basis. Prior to treatment, the patient had been experiencing severe headaches and fatigue, along with mild paralysis of the upper and lower limbs on the right side. At discharge, his symptoms had improved dramatically. His only remaining symptoms were upper-right quadrant blindness and mild speech-related difficulties. At the time of this writing, the patient had experienced sustained tumor reduction over 28 weeks and was nearly in radiographic complete remission (Fig. 3I–L). Even 29 weeks after LMM onset, his Karnofsky Performance Scale score remained at 90.

Cancer Genomic Profiling

Comprehensive genetic cancer profiling was conducted to identify other gene mutations and fusion genes in the resected tumors. This analysis was performed using the GenMineTOP system (Konica Minolta REALM), which comprises DNA and RNA hybridization capture-based next-generation sequencing panels. The results revealed the presence of only the *BRAF* mutation (*BRAF* p.V600E, c.1799T>A; variant allele frequency 38.2%). No other gene mutations covered by the panel were detected, and no fusion genes or exon-skipping mutations were observed. The tumor mutation burden of the malignancy was classified as low (0.5 mutations/Mb), and no genomic regions with significant copy number alterations were identified.

Analysis of GBM and BRAF Alterations Using Public Genomic Datasets

To inquire how frequently *BRAF* mutations occur in GBM and how many patients might potentially benefit from this chemotherapy, we conducted an analysis using public data on GBM (The Cancer Genome Atlas [TCGA] Pan-Cancer Atlas).[8] Of 378 GBM samples, 13 samples (3.4%) exhibited genetic alterations in the *BRAF* gene. Of these, 5 cases were *BRAF* V600E, while the others included one each of G596D, P708S, E375* (nonsense), and KLHL7::BRAF (fusion), and 4 cases of copy number gain (amplification) (Fig. 4A). Next, we evaluated whether the BRAF/MEK inhibitor therapy could improve prognosis in patients with BRAF-wildtype GBM using gene expression data from the TCGA-GBM dataset.[9] The lack of large-scale clinical trials investigating the efficacy of BRAF/MEK inhibitor in BRAF-wildtype GBM prompted us to design this analysis. Among 141 cases in the

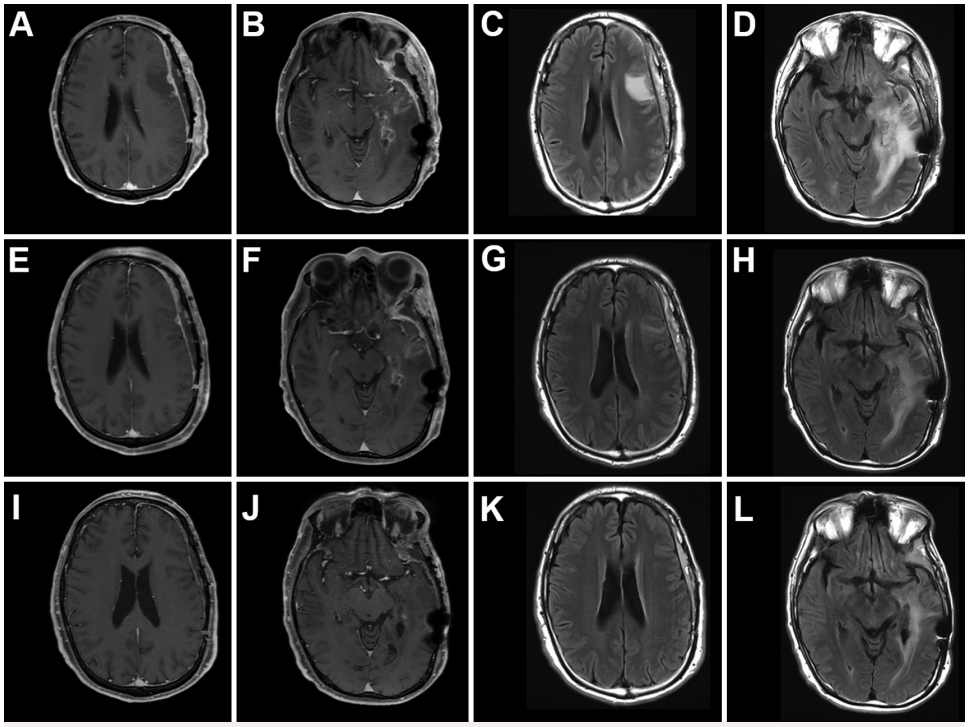

FIG. 3. Imaging changes following the initiation of dabrafenib and trametinib. **A–D:** Axial MR images at the time of tumor dissemination. MRI performed on POD 56 revealed contrast-enhancing lesions with dural enhancement in the left frontal and temporal lobes. FLAIR imaging revealed hyperintense regions surrounding the lesions, indicating perilesional edema. Dabrafenib and trametinib therapy was initiated on POD 74. **E–H:** Axial MR images following the initiation of dabrafenib and trametinib therapy. By day 15 following treatment initiation, the dural contrast enhancement in the left frontal lobe had regressed, and the hyperintense regions on FLAIR imaging in the left frontal and temporal lobes has diminished, suggesting a positive therapeutic response. **I–L:** Axial MR images obtained 28 weeks after the initiation of dabrafenib and trametinib, demonstrating the disappearance of most abnormal contrast-enhancing regions.

dataset with available gene expression data, we excluded 3 cases harboring *BRAF* alterations (TCGA-28-5218-01A: KLHL7::BRAF fusion; TCGA-06-5416-01A: E375*; and TCGA-06-0644-01A: V600E), resulting in a final cohort of 138 cases for analysis. For each case, the average expression value (transcripts per million) of three key genes involved in the BRAF/MEK pathway (*BRAF*, *MAP2K1*, and *MAP2K2*) was calculated and defined as the surrogate "BRAF/MEK pathway expression level." To simulate the potential effect of BRAF/MEK inhibition in BRAF-wildtype GBM, we compared OS between patients with low versus high BRAF/MEK pathway expression levels. When the 138 cases were divided into two equal groups based on the expression level, no significant difference was observed (Fig. 4B). Furthermore, even when mathematically optimizing the cutoff value, no grouping pattern yielded a statistically significant difference.[10] The cutoff with the lowest p value (BRAF/MEK pathway expression level = 61.9) failed to reach statistical significance (Fig. 4C). These findings suggest that in BRAF-wildtype GBM, the activation level of the BRAF/MEK pathway is not associated with prognosis. Thus, the pharmacological inhibition of this pathway may not impact clinical outcomes in this population, as indirectly inferred from our analysis.

Informed Consent

The necessary informed consent was obtained in this study.

Discussion

Observations

We report a case of a high-grade glioma harboring the BRAF V600E mutation that recurred as LMM during initial treatment with TMZ and local irradiation. Following the initiation of combination therapy with dabrafenib and trametinib, the patient exhibited rapid improvement in both clinical symptoms and imaging findings.

Epithelioid GBM is a GBM subtype that was newly defined in the 2016 World Health Organization classification.[2] Currently, the standard treatments for patients with primary epithelioid GBM are TMZ and local radiation therapy, which mirror the standard approach used for all GBMs;[11,12] however, it remains unclear whether sufficient treatment effects are achieved through this approach. The OS rate for patients with primary epithelioid GBM has been reported to be 10.5 months, which is poorer than that for other GBMs.[12] BRAF V600E mutations have been reported to be present in approximately 50% of epithelioid GBM.[13]

Currently, combination therapy with BRAF/MEK inhibitors for tumors with the BRAF V600E mutation represents the standard treatment for several cancer types.[14–17] In recent years, the efficacy of combination therapy using dabrafenib and trametinib has also been reported for gliomas with the BRAF V600E mutation, which has shown very promising results compared with existing treatments.[18–20] These

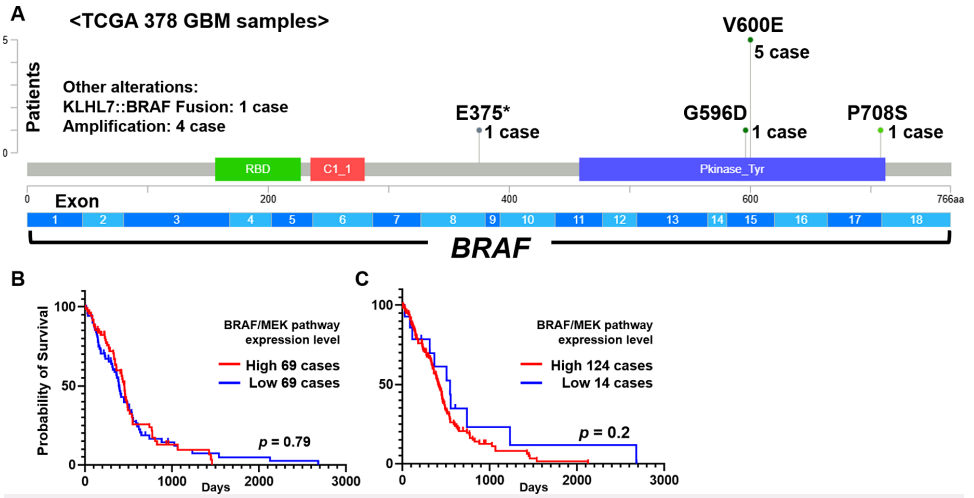

FIG. 4. Analysis of *BRAF* genetic alterations using TCGA data. **A:** Diagram illustrating the mutations on *BRAF* and their locations, along with the number of individuals affected. The analysis was conducted using cBioPortal, analyzing the "mutation" data from the Glioblastoma Multiforme dataset (TCGA Pan-Cancer Atlas, 378 samples). **B and C:** Correlation analysis between BRAF/MEK pathway expression level and prognosis based on TCGA-GBM expression data (log-rank test). Panel B shows the results using a median-based dichotomization, while panel C shows the results using a mathematically optimized cutoff value with the lowest p value.

reports not only suggest the efficacy of these drugs against gliomas but also imply that their CSF penetration, which had been previously lacking detailed studies, is not poor.

The incidence of LMM in high-grade gliomas has been reported to be significant and is generally associated with an extremely poor prognosis.[7] In the present case, early postoperative LMM was observed, and the disease remained refractory despite treatment with TMZ and local radiation therapy. Consequently, the initial prognosis was extremely poor. However, subsequent administration of BRAF/MEK inhibitors has demonstrated significant efficacy. On the occurrence of LMM, our patient developed worsening headache symptoms and symptomatic epilepsy, resulting in deterioration of neurological function and performance status. However, these symptoms rapidly resolved within just 2 weeks of initiating BRAF/MEK inhibitor treatment. The remarkable and sustained improvement observed in the patient's imaging findings was unexpected and surprised both the patient's family and the attending medical team.

We conducted a literature review and identified previously reported cases of GBM that achieved a complete response following treatment with dabrafenib and/or trametinib (Table 1).[21–25] Such reports remain limited, with 8 cases described to date. Among them, LMM was noted in 2 cases, both of which were epithelioid GBM. Our review highlights that even in highly aggressive GBMs, patients harboring specific molecular alterations can achieve a complete response with targeted therapy.

With our analysis of the TCGA dataset, we identified *BRAF* genetic alterations in 3.4% of GBM samples (Fig. 4A). Although the clinical significance of non-V600E alterations and the efficacy of pharmacotherapy for patients harboring these mutations remain uncertain, it is posited that approximately 1%–3% of patients afflicted with this lethal disease could potentially benefit from targeted therapy. On the other hand, our analysis of patients without any *BRAF* alterations indirectly suggested that BRAF/MEK inhibitors are ineffective in BRAF-nonaltered GBM (Fig. 4B and C). While the BRAF/MEK pathway constitutes a central component of the MAPK signaling cascade, which is known to support tumor cell proliferation and invasion, the finding that inhibition of this pathway may not confer a significant survival benefit is puzzling. One hypothetical explanation for this phenomenon is that in BRAF-altered GBM, where the BRAF alteration is likely a driver mutation, tumor growth and progression are highly dependent on the BRAF/MEK pathway. Consequently, blockade of this pathway leads to tumor cell death. In contrast, BRAF-nonaltered GBM may rely on multiple, functionally redundant oncogenic pathways for proliferation and progression. In such cases, inhibition of the BRAF/MEK pathway alone may be insufficient, as compensatory signaling via alternative pathways allows tumor cells to survive.

Our report suggests that a specific subset of patients with high-grade gliomas, including those with LMM, may experience an improvement through BRAF/MEK inhibitor therapy, although previous reports have also documented cases in which the dramatic therapeutic effect of dabrafenib and trametinib combination therapy was only transient.[23,26] At present, data on the efficacy and underlying molecular mechanisms of this treatment remain insufficient. Long-term follow-up of a greater number of cases, along with detailed biological studies on the molecular dynamics of these drugs, is warranted.

Lessons

The combination of dabrafenib and trametinib may be a promising therapeutic option for patients with refractory LMM and high-grade gliomas. This approach has the potential to significantly alter future treatment strategies for these aggressive tumors; however, further large-scale and comprehensive studies are warranted to confirm its clinical utility.

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TABLE 1. Literature review of GBM cases achieving complete response to BRAF/MEK inhibitors

Authors & Year	Age (yrs)/ Sex	Pathology	LMM	BRAF Alteration	IDH Status	BRAF/MEK Inhibitors	Response	PFS From Drug Initiation	Complications
Subbiah et al., 2023[21]	4 cases	High-grade glioma	NA	BRAF V600E	NA	Dabrafenib + trametinib	CR	NA	NA
Kushnirsky et al., 2020[22]	44/M	GBM	No	BRAF V600E	Wildtype	Dabrafenib + trametinib	CR	11 mos (ongoing)	Ischemic stroke
Kanemaru et al., 2019[23]	57/M	eGBM	Yes	BRAF V600E	NA	Dabrafenib + trametinib	CR	4 wks (financial limitations)	No
Burger et al., 2017[24]	25/M	eGBM	Yes	BRAF V600E	Wildtype	Dabrafenib	CR	3 mos (ongoing)	No
Awada et al., 2020[25]	19/M	GBM	No	NA	Wildtype	Dabrafenib + trametinib	CR	13 mos (ongoing)	Creatine increase, acneiform dermatitis, toenail paronychia

CR = complete response; eGBM = epithelioid GBM; NA = not available; PFS = progression-free survival.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Hana, Kawaguchi, Hanakita. Acquisition of data: Hana, Kawaguchi, Murakami. Analysis and interpretation of data: Hana, Kawaguchi, Murakami, Higashi, Hanakita. Drafting the article: Hana, Kawaguchi. Critically revising the article: Hana, Kawaguchi, Hasegawa, Hanakita. Reviewed submitted version of manuscript: Hana, Kawaguchi, Murakami, Hanakita. Approved the final version of the manuscript on behalf of all authors: Hana. Statistical analysis: Hana, Kawaguchi. Study supervision: Hana, Kawaguchi, Hanakita.

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