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Early experience with targeted therapy as a first-line adjuvant treatment for pediatric low-grade glioma

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OBJECTIVE Pediatric low-grade gliomas (pLGGs) frequently exhibit dysregulation of the mitogen-activated protein kinase (MAPK) pathway. Targeted therapies, including mutant BRAF inhibitors (dabrafenib) and MEK inhibitors (trametinib), have shown promise in patients in whom conventional chemotherapy has failed. However, few studies have investigated the use of targeted therapy as a first-line treatment for pLGG. Here, the authors reviewed their institutional experience with using a personalized medicine approach to patients with newly diagnosed pLGGs.

METHODS All pediatric patients at the authors' institution who had been treated with dabrafenib or trametinib for pLGG without first receiving conventional chemotherapy or radiation were retrospectively reviewed. Demographic, clinical, and radiological data were collected.

RESULTS Eight patients underwent targeted therapy as a first-line treatment for pLGG. Five patients had a *BRAF* alteration (1 with a *BRAF*^{V600E} mutation, 4 with a *KIAA1549:BRAF* fusion), and 3 patients had an *NF1* mutation. One of the 8 patients was initially treated with dabrafenib, and trametinib was added later. Seven patients were initially treated with trametinib; of these, 2 later transitioned to dual therapy, whereas 5 continued with trametinib monotherapy. Six patients (75%) demonstrated a partial response to therapy during their treatment course, whereas stable disease was identified in the remaining 2 patients (25%). One patient experienced mild disease progression after completing a course of trametinib monotherapy, but ultimately stabilized after a period of close observation. Another patient experienced tumor progression while on dabrafenib, but subsequently responded to dual therapy with dabrafenib and trametinib. The most common adverse reactions to targeted therapy were cutaneous toxicity (100%) and diarrhea (50%).

CONCLUSIONS Targeted therapies have the potential to become a standard treatment option for pLGG due to their favorable toxicity profile and oral route of administration. This case series provides preliminary evidence that targeted therapies can induce an early disease response as a first-line adjuvant treatment; however, large-scale studies are required to assess long-term durability and safety.

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KEYWORDS pediatric; low-grade glioma; targeted therapy; MAPK; *BRAF*; *MEK*; chemotherapy

Pediatric low-grade gliomas (pLGGs) account for 30% of childhood CNS tumors.[1–3] Gross-total resection results in high long-term survival rates, but may not be possible for gliomas involving eloquent cortex or midline subcortical structures.[1,4] In such cases a variety of adjuvant treatment modalities are available. Chemotherapy options include carboplatin and vincristine or thioguanine, procarbazine, lomustine, and vincristine (TPCV), which result in 5-year overall survival rates approaching 86%[5,6] but can cause hematological abnormalities, central and peripheral nervous system toxicity, and allergic reactions.[5,7] Radiotherapy represents another option and is associated

ABBREVIATIONS IQR = interquartile range; MAPK = mitogen-activated protein kinase; NF1 = neurofibromatosis type 1; NTR = near-total resection; pLGG = pediatric low-grade glioma; RANO = Response Assessment in Neuro-Oncology; STR = subtotal resection.

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with a 6-year progression-free survival of almost 90%, but can result in significant endocrine and neurocognitive complications, particularly in younger patients.[8,9] These conventional therapies are effective at achieving disease remission and prolonging survival, but are associated with significant patient morbidity.

In the current era of personalized medicine, molecularly targeted therapies have emerged as an alternative treatment modality for a subset of pLGGs and have the potential to produce fewer side effects. In particular, inhibitors of the mitogen-activated protein kinase (MAPK) pathway are being explored. Pediatric LGGs frequently exhibit oncogenic overactivation of the MAPK pathway, resulting in sustained cell proliferation.[10] Most commonly, constitutive activation of the MAPK pathway results from *BRAF* gene alterations, including the *BRAF*^{V600E} mutation and the *KIAA1549:BRAF* fusion oncogene.[10,11] Additionally, patients with neurofibromatosis type 1 (NF1) demonstrate a loss of function of neurofibromin, the gene product of *NF1* and a negative regulator of the MAPK pathway; subsequent activation of the MAPK signaling cascade results in tumor formation.[12] Large-scale genomic studies have demonstrated that 68% of pLGGs harbor either a *BRAF*^{V600E} mutation, *KIAA1549:BRAF* gene fusion, or a germline *NF1* mutation.[10] Consequently, selective inhibitors of BRAF and MEK (a downstream member of the MAPK pathway) are promising candidates for the treatment of pLGG.

To date, studies have focused on BRAF and MEK inhibitors as a second-line therapy for pLGGs that have recurred or progressed on standard treatment regimens. Dabrafenib, a specific inhibitor of the *BRAF*^{V600E} mutant, recently demonstrated a 44% response rate and 85% 1-year progression-free survival in phase I/IIa prospective clinical trials,[13,14] and dramatic responses have been described in individual patients.[15] Trametinib, a direct MEK inhibitor, has also demonstrated efficacy as a second-line agent in small retrospective studies of patients with pLGG who had recurrent or refractory disease,[16–18] and larger clinical trials are being planned. However, few studies have investigated the use of dabrafenib or trametinib as a first-line adjuvant therapy for pLGG. Therefore, our objective was to review our institutional experience with a personalized medicine approach to patients with pLGG who underwent individualized treatment with targeted therapy as a first-line modality.

Methods

Study Population

This study was approved by the institutional review board at Connecticut Children's. All patients at our institution who had been diagnosed with pLGG and treated with dabrafenib or trametinib between 2015 and 2020 with at least 1 year of follow-up were included, and their medical records were retrospectively reviewed. Pediatric LGG was diagnosed as follows: 1) via biopsy, or 2) using radiological criteria in patients with NF1. Patients who underwent treatment with standard chemotherapy or radiation therapy prior to targeted therapy were excluded. The following variables were collected: age at diagnosis; sex; NF1 status; reason for imaging; tumor location, size, histology, and grade; genetic mutations; extent of resection; surgical complications; details of adjuvant therapy; interval to tumor recurrence, progression, or death; and need for other adjuvant therapy.

Clinical Management

Primary tumor samples from the surgical biopsy or resection were submitted for mutational analysis via the OncoScan microarray assay (Fig. 1). Treatment recommendations were discussed at our institutional multidisciplinary neuro-oncology tumor board. Patients were offered adjuvant therapy if there was significant residual postoperative disease or tumor progression during an initial observation period. All patients were offered standard chemotherapy with vincristine and carboplatin, and their families were counseled regarding treatment response rates and side effects. Targeted therapy with oral agents was offered as an alternative for patients who had a targetable *BRAF* alteration or a germline *NF1* mutation.

The treatment algorithm is summarized in Fig. 2. Patients and families who chose to pursue targeted therapy were treated with weight-based dosing of trametinib if a *BRAF* fusion or amplification was identified, or if there was a history of NF1 and empirical treatment was being pursued without a biopsy.[19] Patients with a *BRAF*^{V600E}-mutant tumor were treated with weight-based dosing of dabrafenib per the protocol described by Hargrave et al.[13,14,20] Those with disease progression on dabrafenib were offered the option to switch to traditional chemotherapy with vincristine and carboplatin, to switch to trametinib, or to initiate dual therapy with dabrafenib and trametinib.

Outcome Measures

Patients were followed with surveillance MR images approximately every 3 months after treatment was initiated. The clinical response to therapy was assessed using the Response Assessment in Neuro-Oncology (RANO) criteria, with a complete response defined as complete disappearance of all measurable lesions; partial response defined as > 50% reduction in tumor volume; stable disease defined as a < 50% decrease or < 25% increase in tumor volume; and progressive disease defined as a > 25% increase in tumor volume.[21] The baseline scan was defined as the most recent scan prior to the initiation of targeted therapy.

Statistical Analysis

Descriptive statistics were performed, with data reported as median and interquartile range (IQR) for continuous variables and as frequency and percentages for categorical variables. All statistics were calculated in Excel 2019 (Microsoft Corp.).

Results

Patient Population

Twenty-three patients were identified who underwent treatment with targeted therapy during the study period. Thirteen were treated with chemotherapy and/or radia-

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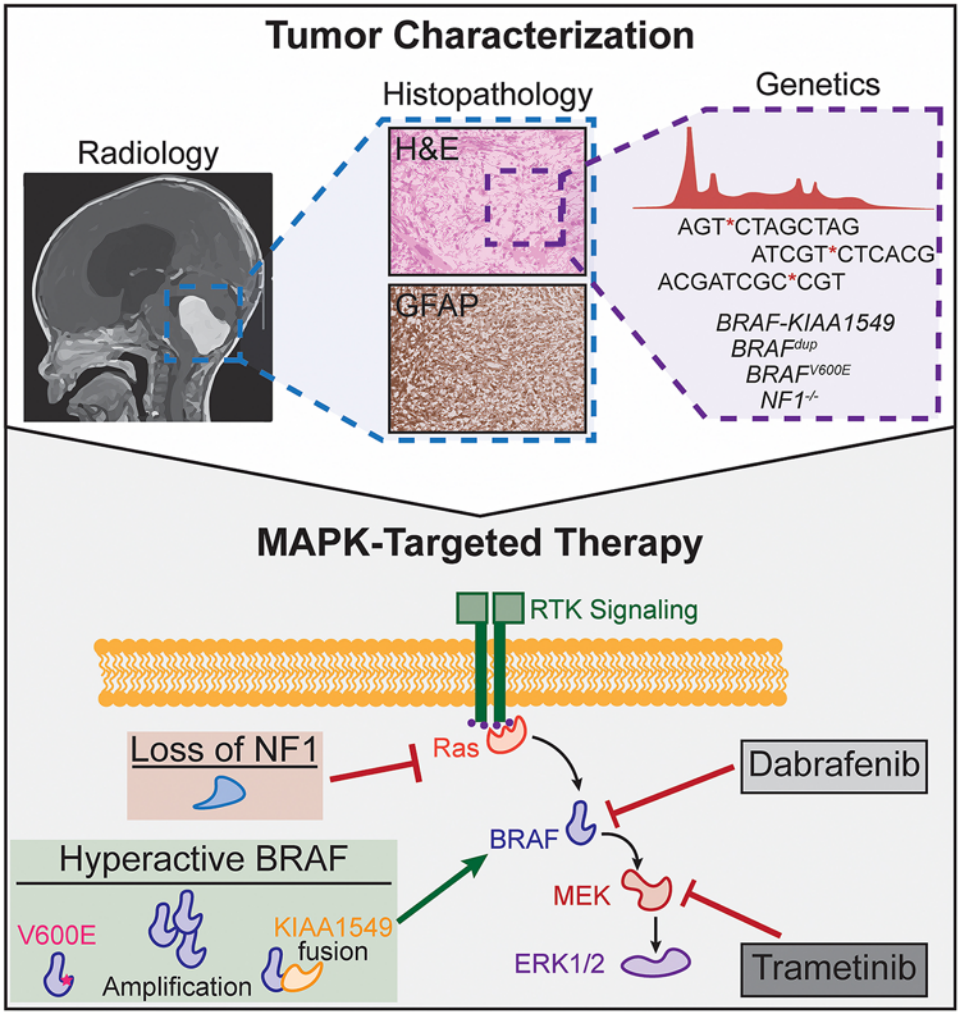

FIG. 1. Personalized treatment approach to pLGGs using MAPK-targeted therapies. Following the initial imaging workup, tumors are resected, debulked, or biopsied for further histopathological and molecular characterization. Patients are then offered first-line treatment with dabrafenib or trametinib in the presence of a targetable *BRAF* alteration or a germline *NF1* mutation. RTK = receptor tyrosine kinase.

tion prior to initiating targeted therapy, and long-term follow-up was not available for 2 patients. The remaining 8 patients were included for further analysis (Fig. 3). The demographic and clinical features of these patients are summarized in Table 1. The most common presenting symptoms included visual changes (38%), headache (13%), emesis (13%), central precocious puberty (13%), gait changes (13%), and torticollis (13%). The median age at diagnosis was 4.3 years (IQR 2.9–8.2 years).

Five patients (62.5%) underwent a surgical procedure to obtain tissue; of these, 2 (40%) were near-total resections (NTRs) and 3 (60%) were biopsies or subtotal resections (STRs). The remaining 3 patients had a history of NF1 and were treated empirically. Of the patients with a tissue diagnosis, 4 (80%) were pilocytic astrocytomas and 1 (20%) was a diffuse leptomeningeal glioneural tumor. All 5 patients from whom tissue was obtained were found to have a *BRAF* alteration (a V600E amino acid substitution was identified in 20%, and a *KIAA1549:BRAF* fusion was present in 80%).

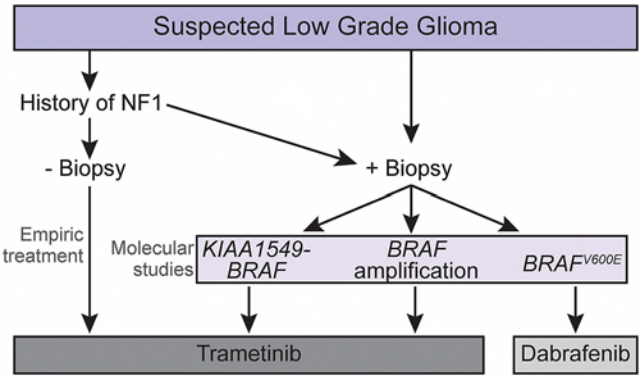

FIG. 2. MAPK-targeted therapy treatment algorithm. Patients with a suspected LGG underwent surgery to obtain biopsy tissue, or were treated empirically in the setting of NF1. Patients with a *BRAF* fusion or amplification were treated with weight-based dosing of trametinib, whereas those with a $BRAF^{V600E}$-mutant tumor were treated with weight-based dosing of dabrafenib. Dabrafenib and trametinib dual therapy is now considered for $BRAF^{V600E}$-mutant tumors as well.

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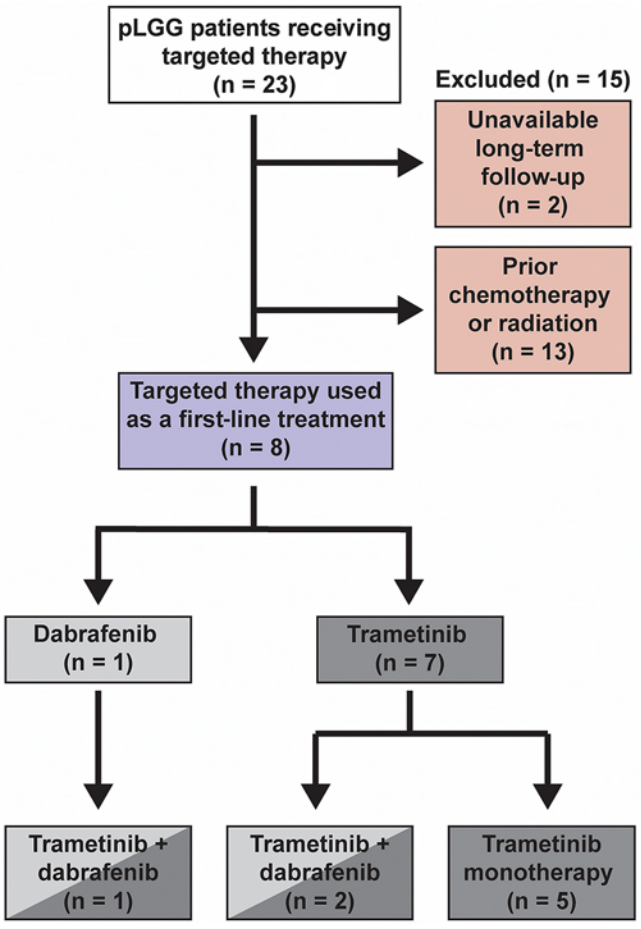

FIG. 3. Summary of patients treated with targeted therapy.

Response to Treatment

Targeted therapy was initiated at a median age of 4.5 years (IQR 3.1–9.5 years). One patient was initially treated with dabrafenib and trametinib was later added. Seven patients were initially treated with trametinib; of these, 2 later transitioned to dual therapy, whereas 5 continued with trametinib monotherapy (Fig. 3). During the study period, 4 patients (50%) completed treatment, with a median duration of treatment of 14.5 months (IQR 13.7–15.0 months). Therapy was discontinued in 2 patients due to adverse effects after 13.4 and 20.1 months, respectively, and they are undergoing continued surveillance. Treatment is ongoing in the remaining 2 patients, who have completed 10.2 and 20.7 months of treatment to date. The median total duration of follow-up for the entire cohort was 14.5 months (IQR 13.0–16.4 months).

The individual radiological responses to treatment are summarized in Fig. 4. Overall, 6 patients (75%) demonstrated a partial response to treatment during their treatment course. An early treatment response was identified on the initial surveillance scan in 4 patients, whereas the other 2 patients demonstrated a response to treatment later in their course. Stable disease was identified in the remaining 2 patients. Two patients demonstrated disease progression after exhibiting an early response to treatment. In one case, mild progression occurred after completing a course of trametinib monotherapy, but her disease stabilized during an extended period of close observation (case 4). In the other case, disease progression was observed while on dabrafenib monotherapy, but the tumor responded to dual therapy with dabrafenib and trametinib (case 8). The same patient experienced a second period of disease progression after dual therapy was paused due to adverse effects; on the resumption of dual therapy, a positive disease response was again identified.

The radiological responses to treatment did not appear to demonstrate clear patterns that correlated with the patients' molecular alterations. Of the 3 patients with NF1, 2 demonstrated a treatment response to trametinib, whereas the third had stable disease without progression. Of the 4 patients with a *BRAF* fusion, 3 demonstrated a treatment response to trametinib; although the fourth patient had mild disease progression on the initial surveillance scan, the tumor subsequently stabilized on continued trametinib therapy. The only patient to have a $BRAF^{V600E}$ mutation demonstrated tumor progression on dabrafenib monotherapy but responded to dual therapy with dabrafenib and trametinib, as described above.

TABLE 1. Demographic, clinical, and pathological characteristics of 8 patients with pLGG

Case No.	Sex	Age at Dx (yrs)	Presenting Symptoms	Tumor Location	EOR	Histological Subtype	Mutation
1	M	7.8	Central precocious puberty	Hypothalamus, 3rd ventricle	NA	Unknown	*NF1*
2	F	4.1	Visual changes	Lt optic nerve	NA	Unknown	*NF1*
3	F	9.2	Visual changes	Lt fornix & thalamus	NA	Unknown	*NF1*
4	F	3.4	Gait changes	4th ventricle	NTR	Pilocytic astrocytoma	*KIAA1549:BRAF* fusion
5	M	4.5	Visual changes	Sellar/parasellar	STR	Pilocytic astrocytoma	*KIAA1549:BRAF* fusion
6	F	1.3	Torticollis, lt ptosis	Medulla (exophytic)	STR	Pilocytic astrocytoma	*KIAA1549:BRAF* fusion
7	M	11.5	Headaches	4th ventricle	STR	Pilocytic astrocytoma	*KIAA1549:BRAF* fusion
8	M	0.7	Emesis	4th ventricle	NTR	Diffuse leptomeningeal glioneural tumor	$BRAF^{V600E}$

Dx = diagnosis; EOR = extent of resection; NA = not applicable.

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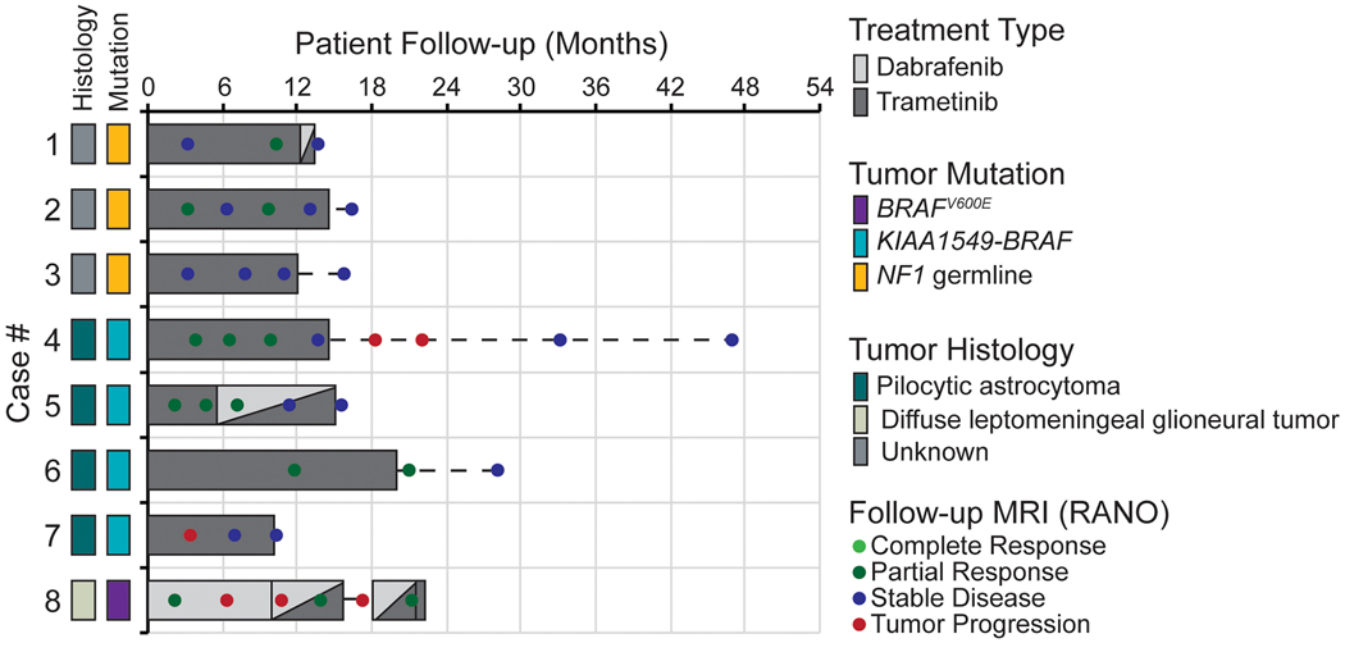

FIG. 4. Individual patient responses to targeted therapy. A total of 8 patients underwent surveillance imaging after initiating targeted therapy. Treatment type, tumor mutation status, and tumor histology are denoted. *Dots* represent each follow-up MRI scan and are color-coded by disease response per RANO criteria. Duration of targeted therapy is represented with *bars*, and duration of follow-up after the completion of treatment is denoted with *dashed lines*.

Clinically, all patients responded well to treatment, with noted improvement or overall stability of their primary symptoms. Of the 3 patients who presented with vision changes, 2 had documented improvements in their vision and 1 demonstrated stable visual deficits over the course of the study.

Adverse Effects

The adverse effects reported by this cohort are summarized in Table 2. All patients experienced cutaneous toxicity, which was mild in 6 cases and improved with dose reduction and/or conservative management using emollient creams or topical steroids. Two patients reported se-

TABLE 2. Adverse reactions associated with targeted therapy in 8 patients with pLGG

Case No.	Treatment	Cutaneous Toxicity	Other Adverse Reactions	Change in Therapy
1a	Trametinib	Yes	None	1-wk pause
1b	Dabrafenib + trametinib	Yes	Distal upper-extremity swelling	Cessation
2	Trametinib	Yes	Chills & night sweats, diarrhea	NA
3	Trametinib	Yes	None	Dose reduction
4	Trametinib	Yes	None	NA
5a	Trametinib	Yes	Diarrhea	Dose reduction
5b	Dabrafenib + trametinib	Yes*	None	NA
6	Trametinib	Yes	Hair loss, diarrhea, oral ulcerations	Cessation
7	Trametinib	Yes	None	NA
8a	Dabrafenib	Yes	None	Addition of trametinib†
8b	Dabrafenib + trametinib	Yes*	Behavioral concerns, diarrhea	Discontinuation of dabrafenib, continuation of trametinib monotherapy

* Cutaneous toxicity persisted but was improved relative to when the patient was being treated with monotherapy.
† Trametinib was added due to disease progression on dabrafenib monotherapy; however, an improvement in the patient's cutaneous toxicity was also noted after initiating dual therapy.

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vere cutaneous toxicity on monotherapy. One (case 5) was subsequently placed on dual therapy with trametinib and dabrafenib, resulting in marked improvement. In the remaining patient (case 1), trametinib was paused for 1 week and then resumed at a reduced dose. Due to continued cutaneous toxicity, he too was placed on dual therapy, but treatment was discontinued 1 month later due to persistent symptoms.

Other adverse reactions included diarrhea (n = 4), chills and night sweats (n = 1), hair loss (n = 1), oral ulcerations (n = 1), behavioral concerns (n = 1), and severe swelling of the distal upper extremities (n = 1). Three patients experienced no adverse effects aside from cutaneous toxicity. In addition to the patient (case 1) whose treatment was discontinued due to severe cutaneous toxicity, a second patient (case 6) required cessation of therapy due to severe oral ulcerations. A third patient (case 8) discontinued dabrafenib but continued on trametinib monotherapy due to persistent behavioral concerns and diarrhea while on dual therapy.

Illustrative Cases

Case 2—NF1

A 4-year-old girl presented with left eye pain and restricted ipsilateral extraocular movements. An ophthalmological examination demonstrated decreased visual acuity of the left eye, optic nerve edema, bilateral Lisch nodules, and multiple café-au-lait spots. MRI demonstrated a left-sided optic pathway glioma, and she was diagnosed with NF1. Treatment with trametinib was initiated and the patient completed 15.5 months of therapy. Follow-up MR images demonstrated a partial disease response and eventually stable disease (Fig. 5A). She continues to be clinically monitored while off therapy, but has demonstrated significant improvements in her vision with stabilization of her optic nerve atrophy.

Case 6—*BRAF* Fusion

A 16-month-old girl with gross motor delays presented with acquired torticollis as well as left-sided ptosis and lacrimation. Workup demonstrated an exophytic mass of the left medulla, and she underwent an STR. Pathological analysis revealed a pilocytic astrocytoma with a *KIAA1549:BRAF* fusion. She was placed on trametinib, and a follow-up MRI study obtained 1 year later demonstrated a partial disease response (Fig. 5B). Trametinib therapy was discontinued after 20 months due to side effects (oral ulcerations), and follow-up MR images demonstrated a stable disease response (Fig. 5B). At her last clinical follow-up she had a nonfocal examination and was meeting her developmental milestones.

Case 8—*BRAF*^{V600E}

A 9-month-old boy presented with macrocephaly and emesis, and an MRI study demonstrated a fourth ventricular mass with diffuse leptomeningeal disease. He underwent an NTR of the posterior fossa component, and pathology was consistent with a *BRAF*^{V600E}-positive diffuse leptomeningeal glioneural tumor. The patient's diffuse leptomeningeal disease initially demonstrated a positive response to dabrafenib, but 11 months after starting treatment he experienced progressive nodular leptomeningeal enhancement (Fig. 5C). Dual therapy with dabrafenib and trametinib was initiated and the patient demonstrated a partial response to therapy 2.6 months later. However, 6 months after starting dual therapy he experienced significant behavioral changes and diarrhea, and his treatment was therefore paused for 3 months. At that point surveillance imaging demonstrated disease progression, and dual therapy was resumed. An MRI study obtained 4 months later again demonstrated a positive disease response and diminished leptomeningeal disease. Unfortunately, he experienced recurrent irritability, behavioral concerns, and diarrhea. Dabrafenib was subsequently discontinued; he remains on trametinib monotherapy and is being closely observed.

Discussion

Advances in genomic sequencing have facilitated a personalized medicine approach by providing a better understanding of the pathways involved in the tumorigenesis of pLGGs. These low-grade tumors are often found to harbor alterations of the MAPK pathway that serve as promising therapeutic targets, including the *KIAA1549:BRAF* fusion (particularly in pilocytic astrocytomas) and the *BRAF*^{V600E} mutation (particularly in pleomorphic xanthoastrocytomas and mixed glioneural tumors).[10,22] Although previous studies have examined the outcomes of targeted therapies for refractory or recurrent pLGGs following conventional chemotherapy and/or radiation, few reports have investigated their potential role as a first-line agent. Nevertheless, targeted therapies are increasingly being offered to patients as an initial treatment strategy.[23] Here we describe our institutional experience with the use of dabrafenib (a selective inhibitor of the *BRAF*^{V600E} mutant) and trametinib (a direct MEK inhibitor) as first-line adjuvant treatments in 8 patients with pLGG. Our preliminary findings suggest that targeted therapy with dabrafenib and/or trametinib can induce an early positive disease response in a subset of patients, with a favorable side effect profile compared to chemotherapy or radiation.

Efficacy of Targeted Therapy for pLGG

Overall, we identified 6 patients (75%) with a partial response to treatment, 4 of whom demonstrated an early response on their initial surveillance scan. Prior studies have focused on the use of targeted therapy for progressive or refractory pLGG, rather than as a first-line treatment. Dabrafenib, which has selective activity against *BRAF*^{V600E}-mutated tumors,[24] can induce a positive disease response in 80% of *BRAF*^{V600E}-mutated pLGGs, resulting in a 3-year progression-free survival of 50%.[25] However, BRAF inhibitors can paradoxically enhance the progression of pLGGs with a *BRAF* fusion; these tumors require treatment with inhibitors of downstream members of the MAPK pathway, such as MEK inhibitors.[26,27] Trametinib, a direct MEK inhibitor, has demonstrated promising results and a good safety profile in early studies,[18,28] with remarkable tumor responses in limited case reports.[17,29] Currently, the TRAM-01 phase II trial (NCT03363217) is planned to

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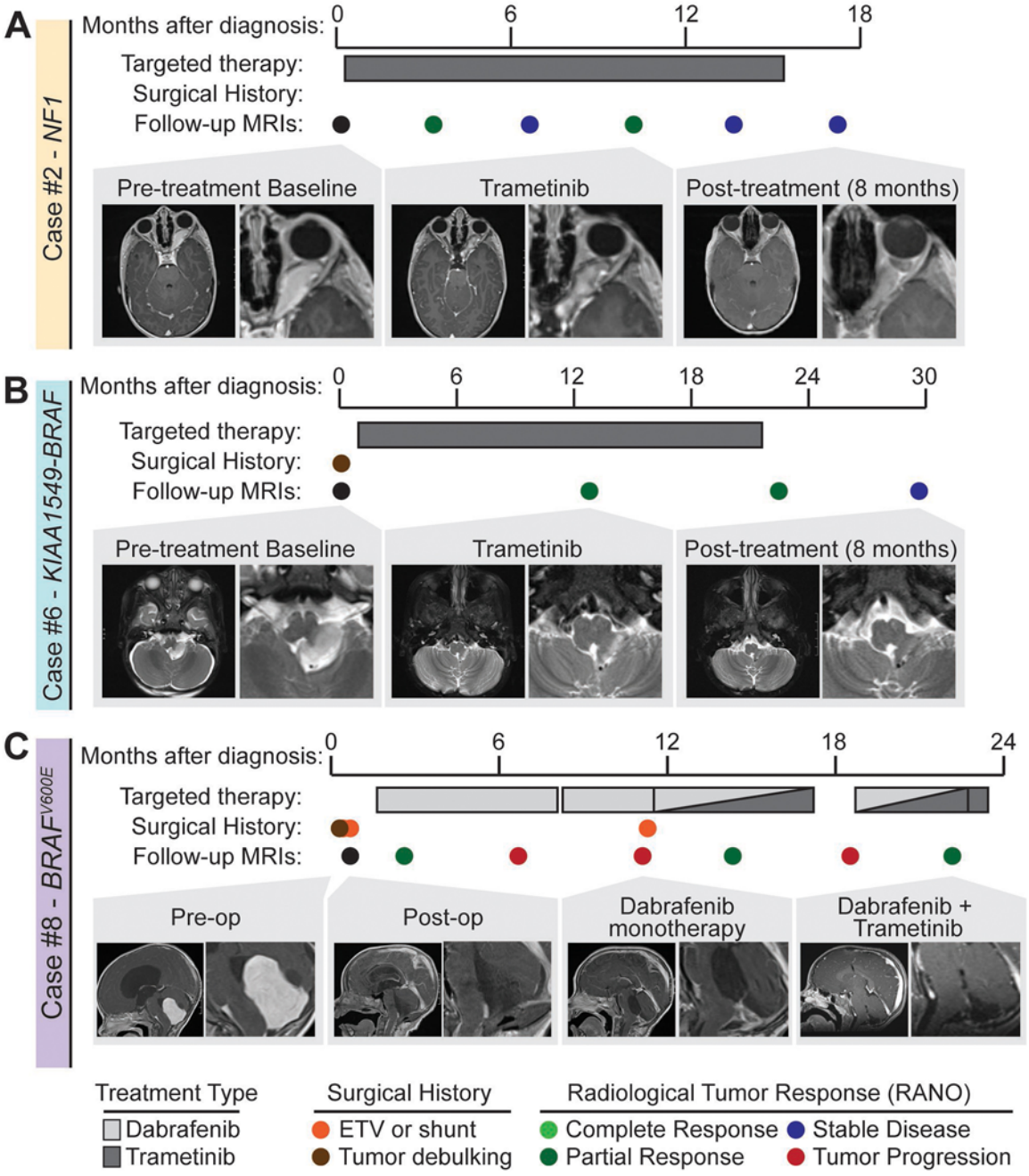

FIG. 5. Illustrative cases depicting the use of targeted therapy. **A:** Case 2. A 4-year-old girl with NF1 underwent 15.5 months of trametinib therapy after an MRI study demonstrated a left-sided optic pathway glioma. Follow-up axial T1-weighted MR images with contrast enhancement demonstrated a partial response to treatment that was sustained following the completion of trametinib monotherapy. **B:** Case 6. A 16-month-old girl with a *KIAA1549:BRAF*-positive lateral medullary pilocytic astrocytoma was treated with 20 months of trametinib therapy following an STR. Axial T2-weighted MR images demonstrated a partial disease response; treatment was ultimately discontinued due to oral ulcerations, but follow-up imaging demonstrated a sustained response. **C:** Case 8. A 9-month-old boy diagnosed with a *BRAF*^{V600E}-positive diffuse leptomeningeal glioneural tumor underwent an NTR of the fourth ventricular component. His treatment course consisted of dabrafenib monotherapy, but he experienced disease progression and was placed on dual therapy with dabrafenib and trametinib. Therapy was subsequently paused for adverse effects and he experienced a rebound effect, followed by another positive disease response when therapy was resumed. ETV = endoscopic third ventriculostomy.

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assess the role of trametinib in the treatment of refractory pLGG in which conventional chemotherapy or radiation have failed.[19] Additionally, the phase III LOGGIC Europe trial will randomize trametinib to carboplatin/vincristine or vinblastine in patients with pLGG requiring additional treatment after their initial surgery, and will be the first to evaluate trametinib as a first-line agent in newly diagnosed patients with pLGG.

One of the patients in our series demonstrated an early response to dabrafenib monotherapy, but ultimately developed progressive disease that responded to the addition of trametinib. This case highlights the potential for acquired resistance to targeted therapy, which may potentially be overcome by targeting a downstream effector. Acquired resistance to dabrafenib in primary brain tumors has been previously attributed to secondary *BRAF* mutations.[30] Although larger studies involving melanoma have demonstrated limited efficacy of trametinib in patients who have acquired resistance to dabrafenib,[31] recent case reports in patients with glioblastoma suggest a therapeutic response to the combination of dabrafenib and trametinib following failed BRAF inhibitor monotherapy.[32,33] An alternative strategy is to treat tumors with a *BRAF*^{V600E} mutation with combination therapy up front, rather than taking a stepwise approach. A phase II trial that involved adult patients with recurrent or progressive low-grade and high-grade gliomas recently highlighted the benefits of dual therapy with dabrafenib and trametinib.[34] In light of these results, we now consider dual therapy as an alternate option.

In addition to dabrafenib and trametinib, other therapies that target the MAPK pathway are also currently under investigation. Vemurafenib, a BRAF inhibitor, has had positive results in phase I clinical trials of recurrent pLGG, and phase II trials are underway.[35] A series that described the use of vemurafenib in 7 patients with pLGG, including first-line treatment in 6 of these patients, demonstrated positive disease responses in 4 patients and stable disease in 1 patient.[36] Furthermore, the MEK inhibitor selumetinib has been shown to be safe and effective in the treatment of *BRAF*-mutated pLGGs and plexiform neurofibromas associated with NF1.[37–39] Additional phase III clinical trials are underway to compare the efficacy of selumetinib as a first-line agent to carboplatin and vincristine (NCT03871257, NCT04166409).

Targeted Therapy for NF1-Associated Tumors

Many centers have also begun to use targeted therapy for the treatment of tumors associated with NF1, even in the absence of a biopsy to confirm a molecular target. *NF1* mutations are known to result in overactivation of the MAPK pathway, and MEK inhibitors have recently received FDA approval (selumetinib) or are currently being investigated in clinical trials (trametinib, mirdametinib) for the treatment of plexiform neurofibromas.[19,40,41] Trametinib is currently being tested in phase II clinical trials for the treatment of progressive or recurrent pLGG associated with NF1,[19] and has demonstrated efficacy in smaller studies.[16] Similarly, in our series we identified partial disease responses to trametinib in 2 patients with NF1, and stabilization of disease in a third.

Durability of Treatment Response

A "rebound" effect after the completion of therapy has been previously reported, with rapid tumor growth occurring in some patients at a median of 2–3 months following the cessation of targeted therapy.[17,25] We experienced similar rebound effects in 2 of our patients who demonstrated tumor progression following the cessation of therapy (Fig. 4). One of these patients (case 4) had mild disease progression following the completion of trametinib monotherapy that eventually stabilized with long-term follow-up. The other patient (case 8) required dual therapy to be paused for approximately 3 months due to adverse effects, and subsequently experienced tumor progression. Interestingly, once back on therapy, there was a rapid disease response, suggesting that MAPK-targeted therapies may require prolonged dosing strategies. Nevertheless, the durability of the therapeutic response will require further follow-up and larger patient cohorts.

Adverse Reactions

In addition to its oral route of administration, one of the primary advantages of targeted therapy is that it has been associated with relatively mild adverse reactions compared with conventional chemotherapy. However, adverse effects do occur and are sometimes severe enough to prompt a pause or discontinuation of treatment. Cutaneous toxicity, in particular, is a well-documented reaction to MAPK-targeted therapies including trametinib and dabrafenib.[42,43] In most cases, treatment-associated rashes can be ameliorated with supportive care and dose reduction.[44] Cutaneous toxicity resulting from a paradoxical increase in ERK activity can also be overcome with dual therapy.[44,45] In our series, all patients experienced cutaneous toxicity, which was successfully managed with supportive care or dose reductions in 6 cases; in the remaining 2 patients, dual therapy was initiated.

Limitations

Our early experience with targeted therapy as a first-line treatment of pLGG is encouraging, but the current study is limited by its retrospective nature and small sample size. Due to the relatively recent introduction of targeted therapy at our institution, our long-term follow-up remains limited, and our results can only be used to comment on the early response to targeted therapy. Further studies are needed to assess the durability of this response as well as the appropriate duration of therapy. In addition, outcomes following targeted therapy must be compared to those of patients treated with standard chemotherapy and/or radiation to determine if targeted therapy is truly a reasonable first-line approach. Although our institutional experience can be compared to historical controls, prospective randomized trials that assess targeted therapies as first-line treatments for pLGG are ultimately needed to establish their efficacy and safety and to optimize treatment paradigms for this patient population.

Conclusions

Although BRAF and MEK inhibitors have previously been demonstrated to be efficacious for patients with

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pLGG who have recurrent or refractory disease, our findings provide preliminary evidence that they may also be considered as a first-line treatment option in newly diagnosed patients, and may have a favorable toxicity profile compared to standard chemotherapy options. Prospective, large-scale studies are indicated to demonstrate the long-term efficacy and safety of targeted therapies as a first-line treatment strategy for pLGG.

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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: Hersh, Gillan. Acquisition of data: Leclair, Lambert, Knopf, Amin. Analysis and interpretation of data: Hersh, Leclair, Lambert, Roche, Gillan, Wrubel. Drafting the article: Hersh, Leclair, Lambert. Critically revising the article: Hersh, Leclair, Lambert, Roche, Gillan, Gell, Lau, Wrubel, Knopf, Anderson, Martin, Bookland. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Hersh. Statistical analysis: Leclair. Administrative/technical/material support: Anderson. Study supervision: Hersh, Gillan.

Supplemental Information

Previous Presentations

This work was presented as an electronic poster at the 2021 AANS Annual Scientific Meeting in Orlando, FL.

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