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New treatment modalities in NF-related neuroglial tumors

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Abstract

The management of low-grade gliomas (LGGs) and other neuroglial tumors in children with neurofibromatosis type 1 (NF1) has not changed over the past 2–3 decades. With the widespread utilization of chemotherapy for younger children with progressive LGGs, outcomes have been good for most patients who have required treatment. However, some may progress after the initiation of chemotherapy and others, although radiographically responding or with stable disease, may develop progressive neurologic and visual deterioration. Molecular-targeted therapy has become an option for patients who have progressed after receiving chemotherapy and the mTOR inhibitors and bevacizumab have already shown some degree of efficacy. However, the greatest impact has been the introduction of the MEK inhibitors. A variety of different MEK inhibitors are in clinical trials and have already demonstrated the ability to result in radiographic tumor shrinkage in the majority of children with NF1 and progressive LGGs. Because of this efficacy, the MEK inhibitors have moved rapidly from phase I studies to ongoing phase III studies comparing their benefit directly to that of chemotherapy. The long-term ability of these agents to not only control disease, but improve visual and/or neurological function, as well as their short- and long-term safety, are open questions that can only be answered by well-constructed prospective, often randomized, clinical trials.

Keywords Neurofibromatosis type 1 · Low-grade glioma · Molecular-targeted therapy · MEK inhibitors · Bevacizumab

Introduction

The treatment of childhood low-grade gliomas (LGGs) has been essentially unchanged over the past 25 years [1, 2]. After initial decisions concerning the need for treatment, therapy has conventionally consisted of attempts of gross total removal of the tumor, if considered feasible, and subsequent consideration of radiation or chemotherapy dependent on a variety of different factors including age of the child, extent of the lesion, and the risk of impeding neurologic or visual compromise. For many young children and increasingly for those who are older, especially pre-pubertal patients, chemotherapy has been increasingly utilized instead of radiation therapy in attempts to delay, and in many cases, obviate the need for radiotherapy [1, 2]. The decision to replace or delay radiotherapy with chemotherapy was often successful, but at times resulted in deleterious outcomes, especially as regards functional neurologic status [1, 2]. As more focused radiation therapy techniques became available, its earlier use has become a somewhat greater option.

In children with neurofibromatosis type 1 (NF1), the rationale to delay, or if possible, eliminate the need for radiation therapy was even stronger [3–5]. Retrospective reviews have suggested that radiotherapy in children with NF1 is associated with a higher likelihood of development of secondary high-grade tumors [3, 4]. In addition, since many of the NF1-associated LGGs which require treatment arise deep in the brain, especially in the chiasmatic/hypothalamic region, the use of radiotherapy has been associated with risk of the development of vascular damage, including Moyamoya disease [5]. Furthermore, many children with NF1 have intellectual challenges which can be worsened by the deleterious effects of radiation therapy on the developing nervous system.

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The use of chemotherapy clearly changed outcome for many patients with NF1-associated LGGs. As will be discussed in detail, many patients benefited with stability and often shrinkage of disease and for the majority, relatively long-term disease control. However, chemotherapy was not as successful in improving neurologic or visual function and for those with visual pathway gliomas and visual dysfunction [1, 2, 6]. One-third of those with NF1 and LGGs experience tumor progression within 5 years of stopping chemotherapy [6]. There is a general consensus that more effective treatment approaches are needed.

Molecular-targeted therapy has over the past 2 decades become an alternative modality of treatment for children with LGGs including those with NF1 [7]. Bevacizumab and the mTOR inhibitors have demonstrated some degree of utility, as will be discussed [8]. Clearly the greatest advance has been the introduction of agents which inhibit the increased aberrant RAS-MAPK signaling underlying the pathogenesis of NF1-related LGGs [9–11]. The MEK inhibitors have quickly moved from phase I studies to ongoing prospective phase III studies: studies comparing their efficacy to conventional chemotherapy for children with progressive NF1-related LGGs. In addition, the studies that are now being performed not only assess the ability of the agent chosen to halt or shrink disease but also to determine the effectiveness of the therapy employed to improve or at least stabilize neurologic and/or visual function.

Clinical aspects of NF1 low-grade gliomas

LGGs are found in approximately 20% of children with neurofibromatosis type 1 (NF1) [12–15]. The vast majority are diagnosed based on radiographic features without histological confirmation. When histological confirmation has been obtained, pilocytic astrocytomas have been found to make up the vast majority of tumors, although a recent retrospective pediatric study suggested that gangliogliomas are more common than conventionally thought [2]. The majority of NF1-related LGGs arise in the visual pathway, involving one or both optic nerves, the chiasm and contiguous structures such as the hypothalamus, optic tracts, and optic radiations [12–15] (Fig. 1). These lesions, although at times isolated to one or both optic nerves, may also notoriously infiltrate the optic tracks and radiations. Because of the occurrence of vacuolation in the myelin sheaths of pediatric NF-1 patients, which presents as areas of abnormal signal intensity (FASI) seen on MRI throughout the brain in children with NF1, separation of LGGs from these FASI can be difficult and often arbitrary [12–15]. NF-related FASI are encountered throughout the brainstem and cerebellar white matter, the basal ganglia, thalami, and the central white matter tracks of the cerebrum. These FASI never enhance, and are usually round in shape; their T1 signal tends to be higher than that of LGG, and they have little of no mass effect. Lesions that cause significant mass effect enhance with MRI contrast agents and/or cause neurologic deficits; they are usually considered to be true gliomas (Fig. 2). Also, when the lesions radiographically enlarge, they are often considered to be LGGs, although FASI can increase in size in the early childhood years and may not regress until puberty (Fig. 2). The FASI in the posterior fossa tend to appear and evolve ahead of those in the diencephalon; it is common to see lesions enlarge in the basalganglia/thalami while lesions in the cerebellum are receding.

The second most common site of NF1-associated gliomas is the brainstem and once again distinction between true

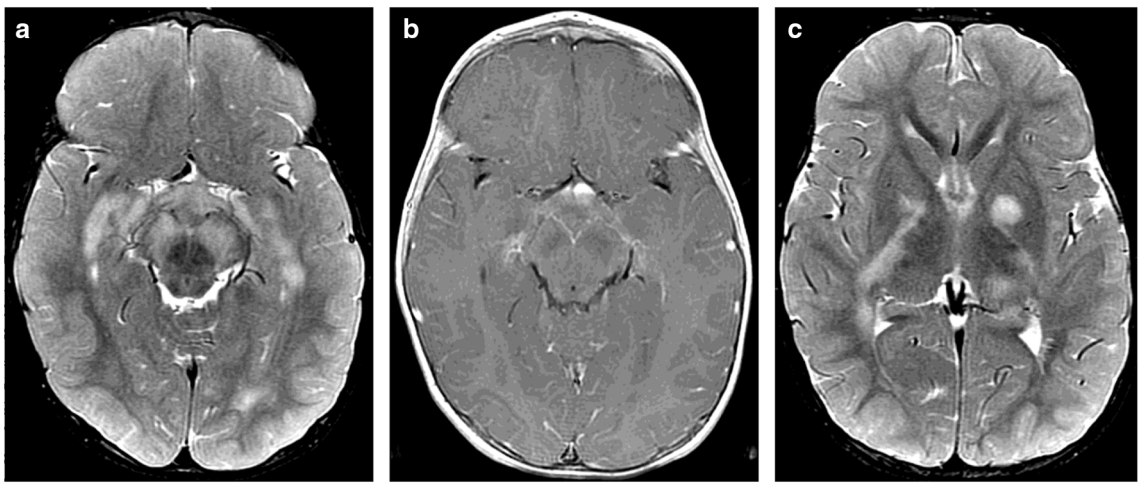

Fig. 1 Infiltrative optic pathway glioma in a 2-year-old, illustrating the difficulty in separating infiltrative tumor from vacuolation. Axial images through the chiasm reveals T2 hyperintense tumor infiltrating of the chiasm, the optic tracts, the medial temporal lobes and the cerebral peduncles (**a**); only a small portion of the chiasmatic component enhances on postcontrast axial T1 image (**b**). Axial T2-weighted image at the level of foramen of Monroe (**c**) shows tumor infiltrating of the bilateral internal capsules (right more than left); the rounded T2 hyperintense lesions in the left globus pallidus and in the posterior left thalamus represented vacuolation

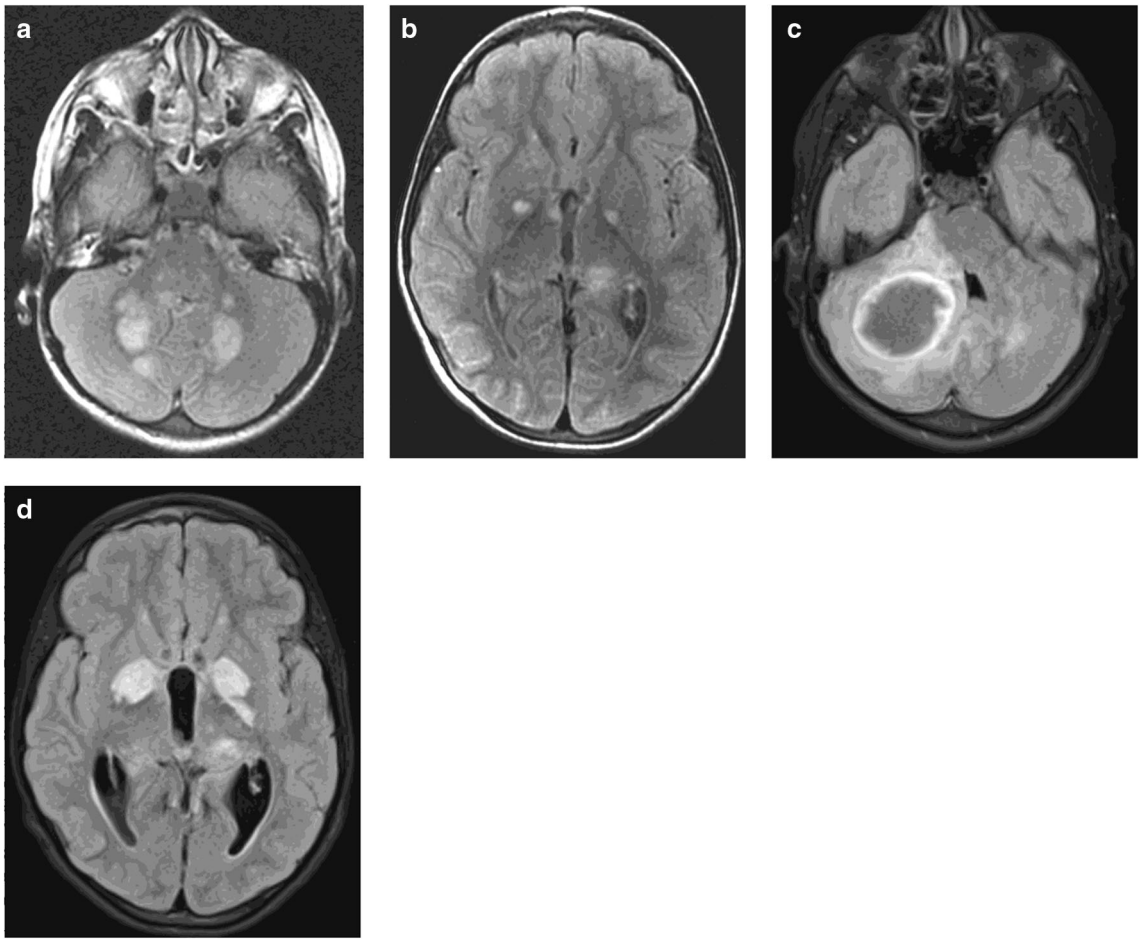

Fig. 2 Temporal evolution of vacuolation and development of a pilocytic astrocytoma within an area of vacuolation.Axial T2 FLAIR images at age 5 years (**a** and **b**) reveal typical hyperintense NF-related vacuolation within the deep cerebellar white matter and middle cerebellar peduncles (**a**); and within the globus pallidus and thalamus (**b**). 4 years later (**c** and **d**), a large pilocytic astrocytoma has developed in the deep right cerebellar hemisphere while vacuolation in the deep left cerebellar hemisphere is slightly decreased (**c**); vacuolation has increased within the bilateral basal ganglia and thalamus (**d**)

brainstem "growing" gliomas and FASI which may expand the brainstem, but not cause neurologic deficits, can be difficult [16]. As the child enters puberty and the teenage years, gliomas may spontaneously stop growing or regress, probably due to biologically driven senescence. In the case of visual pathway gliomas, growth after age 6 is unusual, as is progressive visual loss. LGGs may occur all throughout the brain well into adulthood; however, it is now recognized that NF1-related LGGs in young adults are often more aggressive and may be transformed "piloid astrocytomas" [17, 18].

Since the majority of pediatric NF1-related LGGs are not biopsied or operated on, molecular information on most are not available at the time of diagnosis or treatment. In the case of more aggressive tumors occurring in the teenager and in adults, biological investigations have demonstrated that such "transformed piloid astrocytomas," in addition to harboring inactivating alterations in both NF1 alleles, have acquired other mutations, such as CDKN2A/B mutations and ATRX mutations [17, 18]. For these reasons, it is now recommended that most adults with presumed NF1-associated gliomas undergo at least biopsy to identify the histologic and molecular genetic subtype of the tumor. Occasionally, even in childhood, additional genetic aberrations can be seen children with presumed LGGs which act more "aggressively" and biopsy may be indicated [3, 17, 18].

A major clinical aspect of the care of children with LGGs and NF1 is the decision of when to institute treatment. The majority of patients now are identified on the basis of screening evaluations. The need and yield of such "screening" evaluations are controversial, but are performed in many centers. Patients identified in screening evaluations are often asymptomatic or have static deficits, such as previously unappreciated mild proptosis or strabismus. Children with presumed NF1-LGGs usually have to demonstrate both clinical and radiographic progression to warrant treatment, but the threshold to begin treatment varies greatly among investigators. For some investigators and clinicians growth of a lesion on MRI without clinical worsening is an indication to initiate treatment

especially, if the tumor involves a "critical" portion of the brain. Most will not recommend treatment in patients who have static lesions, even if in eloquent areas of brain. Weighing the risk of treatment versus the likelihood of neurologic or visual deterioration if no treatment is undertaken can be a difficult quandary. The selection of which patients should be treated is of major importance in interpreting clinical trial results, as patient selection clearly can impact the results. Making the situation even more complicated is that NF1-related LGGs, especially those of the visual pathway, tend to be diagnosed in children between the ages of 1 and 4 with NF1; an age where neurologic and especially visual assessments can be quite difficult and often unreliable. This is especially true in children who may have some degree of behavioral, attentional, or developmental challenges, as is often the case in those with NF1. The noted tendency for NF1-associated LGGs to spontaneously stop growing and even involute makes study assessment additionally problematic.

Chemotherapy experience

To appropriately evaluate the potential benefit of new molecular-targeted therapies in the management of NF1-related gliomas, the results of therapy have to be compared to the experience with the use of chemotherapy. In a recent consensus conference publication discussing pediatric LGGs, the outcomes after chemotherapy use for both non-NF1 and NF1 LGGs were reviewed [1, 2]. Since the early 1980s, prospective trials have been undertaken and published including nearly 2000 patients with treatment of naïve LGGs, over 550 of whom were patients with NF1 [2]. A variety of different chemotherapeutic agents have been utilized in these prospective trials; in general, trials have avoided the use of alkylator agents and the most common approach has been the use of the combination of carboplatin and vincristine. Comparison among the trials is difficult because different eligibility criteria were used to determine trial entry, including whether the patient had to have documented progressive disease before initiation of treatment and age. However, despite this variability in study design, results across trials were remarkably similar, as approximately 70% of patients treated with the carboplatin and vincristine regimen had at least stable disease three years following initiation of treatment (treatment varied but usually was undertaken for 12–15 months) and at 5 years, 2 out of every 3 children still did not require any other form of treatment [1, 2, 6]. Overall survivals were also consistent across studies and essentially 100% of patients were alive 5 years from diagnosis. This seeming plateau in the trajectory of loss of disease control between 3 and 5 years of age in children with NF1 may either be due to effectiveness of treatment or to the natural tendency of NF1-associated LGGs to cease growth after 5 to 6 years of age [1, 3, 6]. This tendency to spontaneously cease growth is seen most commonly in diencephalic tumors, including those of the visual pathway. The natural history of brainstem lesions and lesions arising in other parts of the nervous system are less well delineated [1, 2]. Radiographic response rate in these studies was also encouraging, as objective response rate (greater than 50% reduction in the bidirectional diameters of NF1-associated gliomas) was approximately 40% and up to 70% demonstrated some degree of tumor shrinkage.

Since the vast majority of these studies were designed with either progression-free survival or radiographic response as the primary outcome measure, conclusions concerning the efficacy of chemotherapy to improve neurologic or visual function or even to stabilize them are difficult to make. Retrospective visual evaluation was complicated by the young age of many of the patients entered on these studies, the lack of detailed baseline ophthalmologic assessments, and the need to change ophthalmology measures of visual acuity as the child grows [1, 2]. Furthermore, none of the studies prospectively included visual field assessment as an outcome measure [3]. In one retrospective multi-institution review of patients with NF1 and LGGs, it was found that visual outcomes were much more problematic and as less than one-third of patients had improved vision after chemotherapy and approximately another one-third had declining vision despite apparent radiographic stability [19].

Patients with NF1-related LGGs have been treated with agents other than the carboplatin and vincristine alone. A single-agent vinblastine was used in 54 patients with LGGs including 13 with NF1 [20]. A 5-year progression-free survival in the vinblastine study was of similar to that seen in the carboplatin and vincristine trials and radiographic response seemed somewhat less; however, it is difficult to draw any real conclusions given the small sample size [1, 2, 20]. A single-agent temozolamide has also been used, but overall has infrequently resulted in objective response in those treated and also has the drawback that it is an alkylator (alkylators are generally avoided in children with NF1 because of the risk of mutagenesis) [2].

mTOR Inhibitors

The mTOR inhibitors were the first molecularly targeted class of agents utilized in LGGs; however, overall few children with NF1 have been treated [21]. Rapamycin was demonstrated to be effective in giant-cell astrocytomas and pilocytic astrocytomas in children with tuberous sclerosis [21]. Given evidence in one animal model that aberrant signaling of PI3-K pathway was present in NF1 LGGs, a prospective phase II trial of RAD001, a TORC1/TORC2 inhibitor, was undertaken by the Department of Defense Neurofibromatosis Clinical Trial Consortium (DoDNFCTC). This trial was run concurrently

with an industry sponsored trial evaluating RAD001 in non-NF1 patients with LGGs. The early results in the non-NF1 patient population demonstrated some activity, as the majority of children had relatively prolonged stable disease while on drug. Objective radiographic responses were seen in approximately 20% [7]. The results of the non-NF1 LGG study suggested that mTOR inhibitors had some degree of efficacy, but probably less than that of chemotherapy or other molecularly targeted agents. Results of the NF1-associated LGG study are accepted for publication and are similar to those seen in the non-NF1 LGG study.

Because of the toxicity of mTOR inhibitors is usually relatively non-overlapping with many of the agents presently under study, there has been interest in combining them with other agents. A study combining rapamycin with the EGFR inhibitor, tarceva, demonstrated that of the 10 children with NF1 treated, 9 had stable disease for greater than a year while on treatment, and one had a dramatic near total response [22].

Bevacizumab

A somewhat surprising drug which has significant activity in progressive LGGs, including those with NF1, is the antiangiogenic drug bevacizumab. Bevacizumab, approved for use in adults with glioblastoma multiforme, did not demonstrate benefit for children with high-grade gliomas [23]. The biologic rationale for its use in LGGs of childhood, whether in children with NF1 or those without, is questionable; one unpublished study demonstrated increased vascular endothelial growth factor receptor expression in the majority of pediatric LGGs. It was with this limited background that bevacizumab was used in combination with irinotecan in a series of 10 children with LGGs including those with NF1, who had failed multiple other forms of therapy including carboplatin and vincristine and even radiotherapy (as essentially a desperation approach) [8]. Five of the initial 10 patients treated demonstrated a greater than 50% radiographic response, based on the T2-weighted images not just the enhanced images, and clinical improvement in was documented 6 of those treated. This clinical improvement included visual improvement and in two patients this improvement occurred despite long standing loss of both acuity and visual field. A subsequent national study performed by the Pediatric Brain Tumor Consortium (PBTC) demonstrated a near 40% partial response rate in children with LGGs, including those with NF1 [24].

Bevacizumab can be associated with significant toxicities including growth plate damage, the development of ovarian cysts, proteinuria, and hypertension. Usually prolonged use is limited by either the proteinuria or hypertension, although some patients will tolerate the bevacizumab for well over a year in schedules other the 10 mg/kg dosing every 2 weeks which is used at initiation of treatment. Prolonged use is better tolerated at one-half doses, especially when given every 3 weeks.

A major limitation of bevacizumab is "rebound" or at least relapse within weeks (usually 6–12) after stopping the drug. Interestingly, such "rebound" may be associated with continued stabilization of the visual or neurologic improvement despite apparent partial regrowth of the tumor [25]. One of the most important findings of the bevacizumab experience has been that some of the conventional thoughts concerning the ability of therapy to result in clinical improvement, especially in patients with relatively longstanding neurologic or visual compromise, were likely incorrect.

Bevacizumab remains a useful drug in the armamentarium of treatment of NF1-related LGGs, primarily when there is impending or documented acute neurologic dysfunction or visual loss. How best to integrate bevacizumab into treatment regimens remains under study. There is an ongoing clinical trial comparing vinblastine to vinblastine and bevacizumab in newly diagnosed patients with LGGs, including with those with NF1. This study is utilizing co-primary outcome measures of vision and/or neurologic function and progression-free survival. There is also interest in coupling bevacizumab with the MEK inhibitors, although there are concerns of overlapping toxicities, especially hemorrhage and other vascular complications.

The MEK Inhibitors

Of all the molecular-targeted therapies being utilized in patients with NF1-associated LGGs none has engendered the excitement as the use of the MEK inhibitors (Fig. 3). After the discoveries by Pfister and colleagues that aberrations in the RAS-MAPK pathway underlied the majority of LGGs, with over 80% of patients with pilocytic astrocytomas demonstrating BRAF fusions and LGGs in other region of brain and mixed neuroglial tumors commonly having BRAF v600E mutations, the approach to LGGs and low-grade neuroglial tumors, dramatically changed [9–11]. NF1-associated LGGs became a target for treatment with drugs which interfered with RAS-MAPK signaling, as the biallelic loss of NF1 function results in increased aberrant signaling of pathway [26, 27]. In the majority of non-NF1 pilocytic astrocytomas, as well as NF1-associated LGGs, other mutations resulting in aberrant signaling through other pathways were not present. Thus, as a single mutation disease, NF1-associated gliomas were especially attractive targets for treatment. The availability of the MEK inhibitors, which inhibited RAS-MAPK signaling one-step distal to BRAF, facilitated the development of clinical trials. Through the PBTC, a phase I study of the MEK inhibitor selumetinib was completed, despite initial concerns of the potential of retinal venous occlusion secondary to MEK inhibitor therapy [28]. The phase I trial was successfully

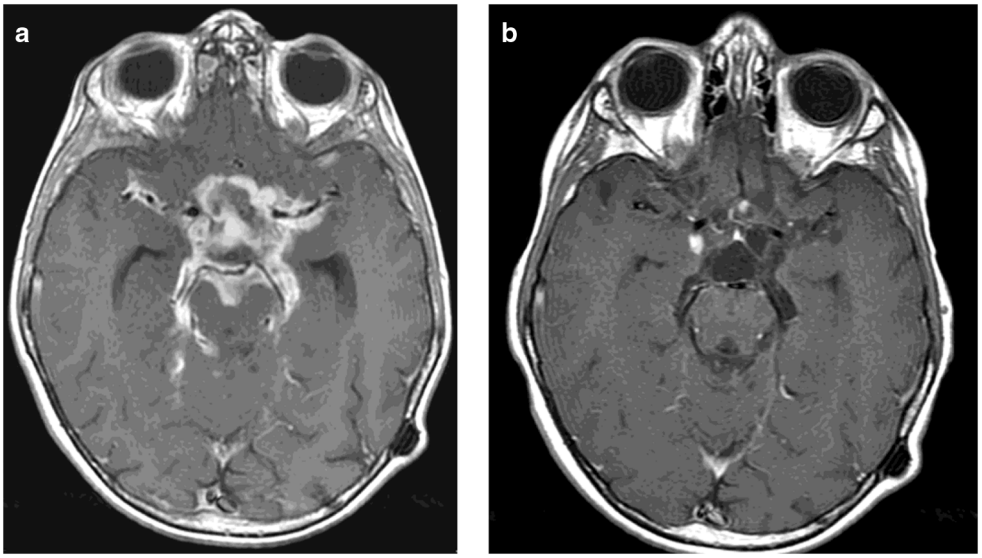

Fig. 3 Response to MEK inhibitor. An extensive chiasmatic/hypothalamic pilocytic astrocytoma is evident, with tumor extending in the subarachnoid spaces of the lateral fissures and the suprasellar/interpeduncular/perimesencephalic cisterns (**a**). Same patient 9 months after initiation of treatment with MEK inhibitor (**b**): near-complete response is evident, 3 small enhancing tumor nodules persist

completed and toxicities seen were different than those usually associated with chemotherapy. Neutropenia, thrombocytopenia, hepatotoxicity, and nephrotoxicity were not frequently encountered. The most common side effect was rash which could be severe and for some patients a reason to stop therapy. This acneiform rash was most marked in children nearing or in puberty. Gastrointestinal toxicity was also encountered, but was usually not dose-limiting. Despite these toxicities, the therapy was relatively well tolerated and in a phase I study a remarkably good response rate was noted, as 5 of 25 of patients had a sustained partial response (greater than 50% tumor shrinkage) associated with a 2-year progression-free survival of 68 ± 9%.

This has resulted in a phase II trial, once again in children both with and without NF1 and non LGGs, also performed through the PBTC [29]. The NF1 stratum of 25 patients has been reported and once again response was highly encouraging with 40% of children having a partial response and essentially 100% of children with NF1 showing some degree of tumor shrinkage. The 2-year progression-free survival was 96 ± 4% and 16 of 25 completed all prescribed therapy. Two of 18 patients with visual pathway tumors had visual acuity improvement, one other demonstrated improvement in visual field, and none worsened. A major question in the NF1 cohort was the sustainability of response after cessation of treatment and early results suggest that well over one-half of patients maintained their response for greater than 6 months, many for greater than a year after stoppage of therapy. In patients who progressed after stopping of treatment, retreatment was allowed and the majority responded again.

The favorable results of this phase II trial has led to the rapid development of a phase III trial now open internationally through the Children's Oncology Group and soon through the International Society of Pediatric Oncology (SIOP) comparing the MEK inhibitor selumetinib, to carboplatin and vincristine for newly diagnosed patients with NF1 and progressive LGGs. This trial is utilizing a 2:1 randomization, as two-thirds of the patients will receive the molecular-targeted therapy. Both progression-free survival and visual/neurologic outcomes are measures of outcome on this prospective, randomized study.

Other MEK inhibitors have been or are still ongoing evaluation in children with NF1 and associated LGGs. A trial has recently been completed with trametinib in children with NF1 and either progressive LGGs or plexiform neurofibromas; results are pending [30]. Binimetinib has just completed phase I studies and is near completion of a phase II study in children with NF1 and LGGs being done through the Department of Defense Clinical Trials Consortium [31]. Cobimetinib is another MEK inhibitor undergoing a drug company–sponsored testing. The relative benefits of these drugs are going to be difficult to assess given that none of these trials are comparing one agent to another. It is unclear whether one drug will act like another, since they have different chemical structures (selumetinib and bimimetinib are quite similar).

The assessment of utility of MEK inhibitors in children with LGGs, probably especially in those with NF1-associated LGGs, will not only be dependent on their ability to stabilize or even shrink disease but their relative abilities to improve neurologic or visual function versus the sequelae they may cause. MEK inhibitors drugs have different toxicity profiles than standard chemotherapies, with rash and gastrointestinal toxicity being the most common side effects seen. However, the MEK inhibitors can also result in muscle enzyme elevation, which although usually asymptomatic, can cause significant weakness (predominantly in young children). Other more severe toxicities such as retinal venous occlusion and cardiomyopathy have been either not seen or rarely reported, but may become more frequent as the number of children on studies increase. Finally since the MEK inhibitors

work by interfering the RAS-MAPK signaling pathway, which is critical in brain development, the long-term toxicity of this class of drugs on neurocognitive function is a concern. However, it is also conceivable that MEK inhibition might improve neurocognitive function in children with NF1, as the lack of neurofibromin due to heterozygous NF1 loss in non-tumor brain tissue results in baseline overaction of the RAS-MAPK pathway and enhanced GABA release.

Another caution is the experience with the use of BRAF v600E inhibitors in children with NF1 and LGGs. A first generation inhibitor sorafenib was shown to have a paradoxic effect of increasing tumor growth in one child an NF1-associated LGG, as well as in children with BRAF fusion mutated LGGs [32].

Future prospectives

As experience grows with the use of molecular-targeted therapies for NF1-associated gliomas and neuroglial tumors, there is still a great deal to be learned about the long-term use of these drugs, both as regard long-term disease control and toxicities. It is unclear how long these drugs, such as the MEK inhibitors, need to be utilized and whether these will be lifelong therapies or ones that can be used only for finite periods of time, depending on the drugs ability to have a more permanent effect and for the tumor's tendency to spontaneously slow its growth or arrest. Another approach is to use intermittent therapy schedules, with planned drug holidays. The phenomenon of senescence is an important factor in the slowing of growth of NF1-associated LGGs, and it is unclear how the MEK inhibitors affect senescence.

The treatment of NF1 gliomas which have acquired other mutations, such as the before mentioned CDKN2A/B mutations and/or ATRX mutations, is unsettled. Such tumors may be less responsive to MEK inhibitors, and there is great interest in investigating if the MEK inhibitors can be used safely in combination with other agents to enhance their efficacy. Studies are ongoing coupling the MEK inhibitors with drugs that inhibit autophagy, one proposed mechanism of acquired resistance. Other studies are planning to utilize the MEK inhibitors with conventional chemotherapy (carboplatin or vinblastine). There is rationale for combining the MEK inhibitors with the mTOR inhibitors; however, there are valid concerns over the overlapping potential toxicities, especially gastrointestinal toxicity and weight loss. Similarly, there is interest in combining the MEK inhibitor with bevacizumab or other antiangiogenesis drugs, but with the concern that such combinations may cause a higher incidence of bleeding or vascular damage.

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Compliance with ethical standards

Conflict of interest Dr. Packer is on the Advisory Committee for Novartis and AstraZeneca.

References

1. Packer RJ, Pfister S, Bouffet E, Avery R, Bandopadhayay P, Bornhorst M, Bowers DC, Ellison D, Fangusaro J, Foreman N, Fouladi M, Gajjar A, Haas-Kogan D, Hawkins C, Ho CY, Hwang E, Jabado N, Kilburn LB, Lassaletta A, Ligon KL, Massimino M, Meeteren SV, Mueller S, Nicolaides T, Perilongo G, Tabori U, Vezina G, Warren K, Witt O, Zhu Y, Jones DT, Kieran M (2017) Pediatric low-grade gliomas: implications of the biologic era. Neuro-Oncology 19(6):750–761
2. Jones DTW, Kieran MW, Bouffet E, Alexandrescu S, Bandopadhayay P, Bornhorst M, Ellison D, Fangusaro J, Fisher MJ, Foreman N, Fouladi M, Hargrave D, Hawkins C, Jabado N, Massimino M, Mueller S, Perilongo G, Schouten van Meeteren AYN, Tabori U, Warren K, Waanders AJ, Walker D, Weiss W, Witt O, Wright K, Zhu Y, Bowers DC, Pfister SM, Packer RJ (2018) Pediatric low-grade gliomas: next biologically driven steps. Neuro-Oncology. 20(2):160–173
3. Sharif S, Ferner R, Birch JM, Gillespie JE, Gattamaneni HR, Baser ME, Evans DGR (2006 Jun 1) Second primary tumors in neurofibromatosis 1 patients treated for optic glioma: substantial risks after radiotherapy. J Clin Oncol 24(16):2570–2575
4. de Blank P, Bandopadhayay P, Haas-Kogan D, Fouladi M, Fangusaro J (2019) Management of pediatric low-grade glioma. Curr Opin Pediatr 31:21–27
5. Rosser TL, Vezina G, Packer RJ (2005 Feb 8) Cerebrovascular abnormalities in a population of children with neurofibromatosis type 1. Neurology. 64(3):553–555
6. Ater JL, Xia C, Mazewski CM, Booth TN, Freyer DR, Packer RJ, Sposto R, Vezina G, Pollack IF (2016) Nonrandomized comparison of neurofibromatosis type 1 and non-neurofibromatosis type 1 children who received carboplatin and vincristine for progressive low-grade glioma: a report from the Children's Oncology Group. Cancer 122:1928–1936
7. Kieran MW, Yao X, Macy M et al (2013) A prospective multi-institutional phase II study of everolimus (RAD001), an mTOR inhibitor, in pediatric patients with recurrent or progressive low-grade glioma. A POETIC Consortium trial. Pediatr Blood Cancer 60(Suppl.3):19–20
8. Packer RJ, Jakacki R, Horn M, Rood B, Vezina G, MacDonald T, Fisher MJ, Cohen B (2009) Objective response of multiply recurrent low-grade gliomas to bevicizumab and irinotecan. Pediatr Blood Cancer 52:791–795
9. Pfister S, Janzarik WG, Remke M et al (2008) BRAF gene duplication constitutes a mechanism of MAPK pathway activation in low-grade astrocytomas. J Clin Invest 118(5):1739–1749
10. Jones DT, Kocialkowski S, Liu L et al (2008) Tandem duplication producing a novel oncogenic BRAF fusion gene defines the majority of pilocytic astrocytomas. Cancer Res 68(21):8673–8677
11. Jones DT, Hutter B, Jäger N, Korshunov A, Kool M, Warnatz HJ, Zichner T, Lambert SR, Ryzhova M, Quang DA, Fontebasso AM, Stütz AM, Hutter S, Zuckermann M, Sturm D, Gronych J, Lasitschka B, Schmidt S, Seker-Cin H, Witt H, Sultan M, Ralser M, Northcott PA, Hovestadt V, Bender S, Pfaff E, Stark S, Faury D, Schwartzentruber J, Majewski J, Weber UD, Zapatka M, Raeder B, Schlesner M, Worth CL, Bartholomae CC, von Kalle C, Imbusch CD, Radomski S, Lawerenz C, van Sluis P, Koster J, Volckmann R, Versteeg R, Lehrach H, Monoranu C, Winkler B, Unterberg A,

Herold-Mende C, Milde T, Kulozik AE, Ebinger M, Schuhmann MU, Cho YJ, Pomeroy SL, von Deimling A, Witt O, Taylor MD, Wolf S, Karajannis MA, Eberhart CG, Scheurlen W, Hasselblatt M, Ligon KL, Kieran MW, Korbel JO, Yaspo ML, Brors B, Felsberg J, Reifenberger G, Collins VP, Jabado N, Eils R, Lichter P, Pfister SM, International Cancer Genome Consortium PedBrain Tumor Project (2013) Recurrent somatic alterations of FGFR1 and NTRK2 in pilocytic astrocytoma. Nat Genet 45(8):927–932

12. Rosser T, Packer RJ (2002) Intracranial neoplasms in children with neurofibromatosis type 1. J Child Neurol 17:630–637
13. Campen CJ, Gutmann DH (2018) Optic pathway gliomas in neurofibromatosis type 1. J Child Neurol 33:73–81
14. de Blank PMK, Fisher MJ, Liu GT et al (2017) Optic pathway gliomas in neurofibromatosis type 1: an update: surveillance, treatment indications, and biomarkers of vision. J Neuroophthalmol 37(Suppl 1):S23–S32
15. Khatua S, Gutmann DH, Packer RJ (2018) Neurofibromatosis type 1 and optic pathway glioma: molecular interplay and therapeutic insights. Pediatr Blood Cancer 65
16. Ullrich NJ, Raja AI, Irons MB et al (2007) Brainstem lesions in neurofibromatosis type 1. Neurosurgery 61:762–766; discussion 766-7
17. Reinhardt A, Stichel D, Schrimpf D et al (2018) Anaplastic astrocytoma with piloid features, a novel molecular class of IDH wildtype glioma with recurrent MAPK pathway, CDKN2A/B and ATRX alterations. Acta Neuropathol 136(2):273–291
18. D'Angelo F, Ceccarelli M (2019) Tala, et al. The molecular landscape of glioma in patients with neurofibromatosis 1. Nat Med 25(1):176–187
19. Fisher MJ, Loguidice M, Gutmann DH, Listernick R, Ferner RE, Ullrich NJ, Packer RJ, Tabori U, Hoffman RO, Ardern-Holmes SL, Hummel TR, Hargrave DR, Bouffet E, Charrow J, Bilaniuk LT, Balcer LJ, Liu GT (2012) Visual outcomes in children with neurofibromatosis type 1-associated optic pathway glioma following chemotherapy: a multicenter retrospective analysis. Neuro-Oncology 14:790–797
20. Lassaletta A, Scheinemann K, Zelcer SM, Hukin J, Wilson BA, Jabado N, Carret AS, Lafay-Cousin L, Larouche V, Hawkins CE, Pond GR, Poskitt K, Keene D, Johnston DL, Eisenstat DD, Krishnatry R, Mistry M, Arnoldo A, Ramaswamy V, Huang A, Bartels U, Tabori U, Bouffet E (2016) Phase II weekly vinblastine for chemotherapy-naive children with progressive low-grade glioma: a Canadian Pediatric Brain Tumor Consortium Study. J Clin Oncol 34:3537–3543
21. Krueger DA, Care MM, Holland K, Agricola K, Tudor C, Mangeshkar P, Wilson KA, Byars A, Sahmoud T, Franz DN (2010) Everolimus for subependymal giant-cell astrocytomas in tuberous sclerosis. N Engl J Med 363(19):1801–1811
22. Yalon M, Rood B, MacDonald T et al (2013) A feasibility and efficacy study of rapamycin and erlotinib for recurrent pediatric low-grade gliomas (LGG). Pediatr Blood Cancer 1:71–76
23. Grill J, Massimino M, Bouffet E, Azizi AA, McCowage G, Cañete A, Saran F, le Deley MC, Varlet P, Morgan PS, Jaspan T, Jones C, Giangaspero F, Smith H, Garcia J, Elze MC, Rousseau RF, Abrey L, Hargrave D, Vassal G (2018) Phase II, open-label, randomized, multicenter trial (HERBY) of bevacizumab in pediatric patients with newly diagnosed high-grade glioma. J Clin Oncol 36(10): 951–958
24. Gururangan S, Fangusaro J, Poussaint TY, McLendon RE, Onar-Thomas A, Wu S, Packer RJ, Banerjee A, Gilbertson RJ, Fahey F, Vajapeyam S, Jakacki R, Gajjar A, Goldman S, Pollack IF, Friedman HS, Boyett JM, Fouladi M, Kun LE (2014 Jan) Efficacy of bevacizumab plus irinotecan in children with recurrent low-grade gliomas–a Pediatric Brain Tumor Consortium study. Neuro-Oncology 16(2):310–317
25. Avery RA, Hwang EI, Jakacki RI, Packer RJ (2014) Marked Recovery of visition in children with optic pathway gliomas treated with bevacizumab. Arch Ophthalmol JAMA Ophthalmol 132(1): 111–114
26. Gutmann DH, McLellan MD, Hussain I et al (2013) Somatic neurofibromatosis type 1 (NF1) inactivation characterizes NF1-associated pilocytic astrocytoma. Genome Res 23(3):431–439
27. Gutmann DH, James CD, Poyhonen M et al (2003) Molecular analysis of astrocytomas presenting after age 10 in individuals with NF1. Neurology 61(10):1397–1400
28. Banerjee A, Jackacki R, Onar A et al (2017) A phase I trial of the MEK inhibitor selumetinib (AZD6244) in pediatric patients with recurrent or refractory low-grade glioma: a Pediatric Brain Tumor (PBTC) Study. Neuro-Oncology 19(8):1135–1144
29. Fangusaro J, Onar-Thomas A, Young Poussaint T, Wu S, Ligon AH, Lindeman N, Banerjee A, Packer RJ, Kilburn LB, Goldman S, Pollack IF, Qaddoumi I, Jakacki RI, Fisher PG, Dhall G, Baxter P, Kreissman SG, Stewart CF, Jones DTW, Pfister SM, Vezina G, Stern JS, Panigrahy A, Patay Z, Tamrazi B, Jones JY, Haque SS, Enterline DS, Cha S, Fisher MJ, Doyle LA, Smith M, Dunkel IJ, Fouladi M (2019) Selumetinib in paediatric patients with BRAF-aberrant or neurofibromatosis type 1-associated recurrent, refractory, or progressive low-grade glioma: a multicenter, phase 2 trial. Lancet Oncol 20(7):1011–1022
30. Bouffet EKM, Hargrave D, Roberts S et al (2018) Trametinib therapy in pediatric patients with low-grade gliomas (LGG) with BRAF gene fusion; a disease-specific cohort in the first pediatric testing of trametinib. Neuro-Oncology 20:i114
31. Robison NPJ, Malvar J, Gruber-Filbin M et al (2018) A phase I dose escalation trial of the MEK1/2 inhibitor MEK162 (binimetinib) in children with low-grade gliomas and other RAS/RAF pathways-activated tumors. Neuro-Oncology 20:i114
32. Karajannis MA, Legault G, Fisher MJ, Milla SS, Cohen KJ, Wisoff JH, Harter DH, Goldberg JD, Hochman T, Merkelson A, Bloom MC, Sievert AJ, Resnick AC, Dhall G, Jones DTW, Korshunov A, Pfister SM, Eberhart CG, Zagzag D, Allen JC (2014) Phase II study of sorafenib in children with recurrent or progressive low-grade astrocytomas. Neuro-Oncology 16(10):1408–1416